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Wos et al.

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[54] AROMATIC C_{16}-C_{20}-SUBSTITUTED TETRAHYDRO PROSTAGLANDINS USEFUL AS FP AGONISTS

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[51] Int. Cl.^{6} C07C 405/00; A01K 31/557

[52] U.S. Cl. 514/530; 514/562; 514/567; 514/570; 549/66; 560/12; 560/16; 560/17; 560/43; 562/429; 562/431; 562/457; 562/64; 564/99

[58] Field of Search 560/121, 12, 16, 560/17, 43; 562/431, 429, 457, 621; 514/530, 562, 567, 570; 549/66; 564/99

[56] References Cited

U.S. PATENT DOCUMENTS

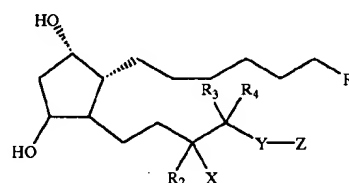|			
3,776,938	12/1973	Bergstrom et al.	260/468
3,966,792	6/1976	Hayashi et al.	260/468
4,004,020	1/1977	Skuballa et al.	424/278
4,011,262	3/1977	Hess	560/118
4,024,179	5/1977	Bindra et al.	260/473
4,051,238	9/1977	Sokolowski	424/181
4,073,934	2/1978	Skuballa et al.	424/305
4,128,720	12/1978	Hayashi et al.	560/9
4,154,950	5/1979	Nelson	560/53
4,206,151	6/1980	Grudzinskas	568/367
4,621,100	11/1986	Lund et al.	514/573
5,166,178	11/1992	Ueno et al.	514/573
5,212,324	5/1993	Ueno	554/118
5,296,504	3/1994	Stjernschantz et al.	514/530
5,302,617	4/1994	Ueno	514/573
5,321,128	6/1994	Stjernschantz et al.	514/530
5,332,730	7/1994	Chan	511/151
5,409,911	4/1995	Tyler et al.	514/91
5,422,368	6/1995	Stjernschantz	514/530
5,422,369	6/1995	Stjernschantz	514/530
5,426,115	6/1995	Ueno et al.	514/438
5,578,618	11/1996	Stjernschantz	514/365
5,587,391	12/1996	Burk	514/357
5,627,208	5/1997	Stjernschantz et al.	514/530
5,665,773	9/1997	Klimko et al.	514/530
5,688,819	11/1997	Woodward et al.	514/357
5,703,108	12/1997	Cameron et al.	514/382
5,834,498	11/1998	Burk	514/445

FOREIGN PATENT DOCUMENTS

0 857 718 A1	6/1997	European Pat. Off. .
002 460 990	7/1976	Germany .
WO 92/02495	2/1992	Germany .
WO 98/12175	3/1998	Japan .
1 456 838	11/1972	United Kingdom .
1 542 569	8/1976	United Kingdom .
WO 95/18102	7/1995	WIPO .
WO 97/23225	7/1997	WIPO .
WO 97/31895	9/1997	WIPO .
WO 98/20880	5/1998	WIPO .
WO 98/20881	5/1998	WIPO .
WO 98/21180	5/1998	WIPO .
WO 98/50024	11/1998	WIPO .

OTHER PUBLICATIONS

Liljebris, C., Selen, G., Resul, B., Stjernschantz, J., and Hacksell, U., "Dervatives of 17–Phenyl–18, 19, 20–trinorprostaglandin $F_{2\alpha}$ Isoppropyl Ester: Potential Antiglaucoma Agents", *Journal of Medicinal Chemistry*, vol. 38, No.2, (1995).

Bundy, G. L., and Lincoln, F. H., "Synthesis of 17–Phenyl–18, 19, 20–Trinoprostaglandins I. The PG_1 Series", *Prostaglandins*, vol. 9, No. 1, (Jan. 1975).

Primary Examiner—Robert Gerstl
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[57] ABSTRACT

The invention provides novel PGF analogs. In particular, the present invention relates to compounds having a structure according to the following formula:

wherein R_1, R_2, R_3, R_4, X, Y, and Z are defined below.

This invention also includes optical isomers, diastereomers and enantiomers of the formula above, and pharmaceutically-acceptable salts, biohydrolyzable amides, esters, and imides thereof.

The compounds of the present invention are useful for the treatment of a variety of diseases and conditions, such as bone disorders and glaucoma. Accordingly, the invention further provides pharmaceutical compositions comprising these compounds. The invention still further provides methods of treatment for bone disorders and glaucoma using theses compounds or the compositions containing them.

28 Claims, No Drawings

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AROMATIC C₁₆-C₂₀-SUBSTITUTED TETRAHYDRO PROSTAGLANDINS USEFUL AS FP AGONISTS
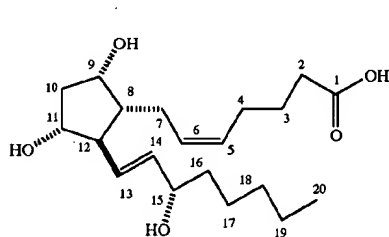
CROSS REFERENCE

This application claims priority under Title 35, United States Code 119(e) from Provisional Application Ser. No. 60/058,217, filed Sep. 9, 1997.

TECHNICAL FIELD

The subject invention relates to certain novel analogs of the naturally occurring prostaglandin. Specifically, the subject invention relates to novel Prostaglandin F analogs. The subject invention further relates to methods of using said novel Prostaglandin F analogs. Preferred uses include methods of treating bone disorders and glaucoma.

BACKGROUND OF THE INVENTION

Naturally occurring prostaglandin (PGA, PGB, PGE, PGF, and PGI) are C-20 unsaturated fatty acids. $PGF_{2\alpha}$, the naturally occurring Prostaglandin F in humans, is characterized by hydroxyl groups at the C_9 and C_{11} positions on the alicyclic ring, a cis-double bond between C_5 and C_6, and a trans-double bond between C_{13} and C_{14}. Thus $PGF_{2\alpha}$ has the following formula:

PGF₂ₐ

Analogs of naturally occurring Prostaglandin F have been disclosed in the art. For example, see U.S. Pat. No. 4,024, 179 issued to Bindra and Johnson on May 17, 1977; German Patent No. DT-002,460,990 issued to Beck, Lerch, Seeger, and Teufel published on Jul. 1, 1976; U.S. Pat. No. 4,128, 720 issued to Hayashi, Kori, and Miyake on Dec. 5, 1978; U.S. Pat. No. 4,011,262 issued to Hess, Johnson, Bindra, and Schaaf on Mar. 8, 1977; U.S. Pat. No. 3,776,938 issued to Bergstrom and Sjovall on Dec. 4, 1973; P. W. Collins and S. W. Djuric, "Synthesis of Therapeutically Useful Prostaglandin and Prostacyclin Analogs", *Chem. Rev.* Vol. 93 (1993), pp. 1533–1564; G. L. Bundy and F. H. Lincoln, "Synthesis of 17-Phenyl-18,19,20-Trinorprostaglandins: I. The PG₁ Series", *Prostaglandin*, Vol. 9 No. 1 (1975), pp. 1–4; W. Bartman, G. Beck, U. Lerch, H. Teufel, and B. Scholkens, "Luteolytic Prostaglandin: Synthesis and Biological Activity", *Prostaglandin*, Vol. 17 No. 2 (1979), pp. 301–311; C. Iiljebris, G. Selen, B. Resul, J. Sternschantz, and U. Hacksell, "Derivatives of 17-Phenyl-18, 19,20-trinorprostaglandin F₂α Isopropyl Ester: Potential Antiglaucoma Agents", *Journal of Medicinal Chemistry*, Vol. 38 No. 2 (1995), pp. 289–304.

Naturally occurring prostaglandin are known to possess a wide range of pharmacological properties. For example, prostaglandin have been shown to: relax smooth muscle, which results in vasodilatation and bronchodilatation, to inhibit gastric acid secretion, to inhibit platelet aggregation, to reduce intraocular pressure, and to induce labor. Although
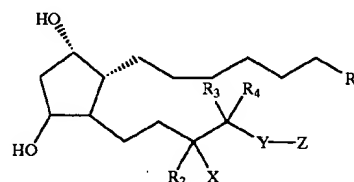
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naturally occurring prostaglandin are characterized by their activity against a particular prostaglandin receptor, they generally are not specific for any one prostaglandin receptor. Therefore, naturally-occurring prostaglandin are known to cause side effects such as inflammation, as well as surface irritation when administered systemically. It is generally believed that the rapid metabolism of the naturally occurring prostaglandin following their release in the body limits some of the effects of the prostaglandin to a local area. This effectively prevents the prostaglandin from stimulating prostaglandin receptors throughout the body and causing the effects seen with the systemic administration of naturally occurring prostaglandin.

Prostaglandin, especially prostaglandin of the E series (PGE), are known to be potent stimulators of bone resorption. $PGF_{2\alpha}$ has also been shown to be a stimulator of bone resorption but not as potent as PGE_2. Also, it has been demonstrated the $PGF_{2\alpha}$ has little effect on bone formation. It has been suggested that some of the effects of $PGF_{2\alpha}$ on bone resorption, formation and cell replication may be mediated by an increase in endogenous PGE_2 production.

In view of both the wide range of pharmacological properties of naturally occurring prostaglandin and of the side effects seen with the systemic administration of these naturally occurring prostaglandin, attempts have been made to prepare analogs to the naturally occurring prostaglandin that are selective for a specific receptor or receptors. A number of such analogs have been disclosed in the art. Though a variety of prostaglandin analogs have been disclosed, there is a continuing need for potent, selective prostaglandin analogs for the treatment of a variety diseases and conditions.

SUMMARY OF THE INVENTION

The invention provides novel PGF analogs. In particular, the present invention relates to compounds having a structure according to the following formula:

wherein R_1, R_2, R_3, R_4, X, Y, and Z are defined below.

This invention also includes optical isomers, diastereomers and enantiomers of the formula above, and pharmaceutically-acceptable salts, biohydrolyzable amides, esters, and imides thereof.

The compounds of the present invention are useful for the treatment of a variety of diseases and conditions, such as bone disorders and glaucoma. Accordingly, the invention further provides pharmaceutical compositions comprising these compounds. The invention still further provides methods of treatment for bone disorders and glaucoma using theses compounds or the compositions containing them.

DETAILED DESCRIPTION OF THE INVENTION

Terms and Definitions

"Acyl" is a group suitable for acylating a nitrogen atom to form an amide or carbamate or an oxygen atom to form an ester group. Preferred acyl groups include benzoyl, acetyl,

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tert-butyl acetyl, para-phenyl benzoyl, and trifluoroacetyl. More preferred acyl groups include acetyl and benzoyl. The most preferred acyl group is acetyl.

"Alkyl" is a saturated or unsaturated hydrocarbon chain having 1 to 18 carbon atoms, preferably 1 to 12, more preferably 1 to 6, more preferably still 1 to 4 carbon atoms. Alkyl chains may be straight or branched. Preferred branched alkyl have one or two branches, preferably one branch. Preferred alkyl are saturated. Unsaturated alkyl have one or more double bonds and/or one or more triple bonds. Preferred unsaturated alkyl have one or two double bonds or one triple bond, more preferably one double bond. Alkyl chains may be unsubstituted or substituted with from 1 to about 4 substituents. Preferred alkyl are unsubstituted. Preferred substituted alkyl are mono-, di-, or trisubstituted. Preferred alkyl substituents include halo, hydroxy, aryl (e.g., phenyl, tolyl, alkyloxphenyl, alkyloxycarbonylphenyl, halophenyl), heterocyclyl, and heteroaryl.

"Aromatic ring" is an aromatic hydrocarbon ring system. Aromatic rings are monocyclic or fused bicyclic ring systems. Monocyclic aromatic rings contain from about 5 to about 10 carbon atoms, preferably from 5 to 7 carbon atoms, and most preferably from 5 to 6 carbon atoms in the ring. Bicyclic aromatic rings contain from 8 to 12 carbon atoms, preferably 9 or 10 carbon atoms in the ring. Aromatic rings may be unsubstituted or substituted with from 1 to about 4 substituents on the ring. Preferred aromatic ring substituents include: halo, cyano, alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof. More preferred substituents include halo and haloalkyl. Preferred aromatic rings include naphthyl and phenyl. The most preferred aromatic ring is phenyl.

"Bone disorder" means the need for bone repair or replacement. Conditions in which the need for bone repair or replacement may arise include: osteoporosis (including post menopausal osteoporosis, male and female senile osteoporosis and corticosteroid induced osteoporosis), osteoarthritis, Paget's disease, osteomalacia, multiple myeloma and other forms of cancer, prolonged bed rest, chronic disuse of a limb, anorexia, microgravity, exogenous and endogenous gonadal insufficiency, bone fracture, non-union, defect, prosthesis implantation and the like.

"Carbocyclic aliphatic ring" is a saturated or unsaturated hydrocarbon ring. Carbocyclic aliphatic rings are not aromatic. Carbocyclic aliphatic rings are monocyclic, or are fused, spiro, or bridged bicyclic ring systems. Monocyclic carbocyclic aliphatic rings contain from about 4 to about 10 carbon atoms, preferably from 4 to 7 carbon atoms, and most preferably from 5 to 6 carbon atoms in the ring. Bicyclic carbocyclic aliphatic rings contain from 8 to 12 carbon atoms, preferably from 9 to 10 carbon atoms in the ring. Carbocyclic aliphatic rings may be unsubstituted or substituted with from 1 to about 4 substituents on the ring. Preferred carbocyclic aliphatic ring substituents include: halo, cyano, alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof. More preferred substituents include halo and haloalkyl. Preferred carbocyclic aliphatic rings include cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl. More preferred carbocyclic aliphatic rings include cyclohexyl, cycloheptyl, and cyclooctyl. The most preferred carbocyclic aliphatic ring is cycloheptyl.

"Halo" is fluoro, chloro, bromo or iodo. Preferred halo are fluoro, chloro and bromo; more preferred are chloro and fluoro, especially fluoro.

"Haloalkyl" is a straight, branched, or cyclic hydrocarbon substituted with one or more halo substituents. Preferred

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haloalkyl are C_1–C_{12}; more preferred are C_1–C_6; more preferred still are C_1–C_3. Preferred halo substituents are fluoro and chloro. The most preferred haloalkyl is trifluoromethyl.

"Heteroalkyl" is a saturated or unsaturated chain containing carbon and at least one heteroatom, wherein no two heteroatoms are adjacent. Heteroalkyl chains contain from 1 to 18 member atoms (carbon and heteroatoms) in the chain, preferably 1 to 12, more preferably 1 to 6, more preferably still 1 to 4. Heteroalkyl chains may be straight or branched. Preferred branched heteroalkyl have one or two branches, preferably one branch. Preferred heteroalkyl are saturated. Unsaturated heteroalkyl have one or more double bonds and/or one or more triple bonds. Preferred unsaturated heteroalkyl have one or two double bonds or one triple bond, more preferably one double bond. Heteroalkyl chains may be unsubstituted or substituted with from 1 to about 4 substituents. Preferred heteroalkyl are unsubstituted. Preferred heteroalkyl substituents include halo, hydroxy, aryl (e.g., phenyl, tolyl, alkyloxphenyl, alkyloxycarbonylphenyl, halophenyl), heterocyclyl, heteroaryl. For example, alkyl substituted with the following substituents are heteroalkyl: alkoxy (e.g., methoxy, ethoxy, propoxy, butoxy, pentoxy), aryloxy (e.g., phenoxy, chlorophenoxy, tolyloxy, methoxyphenoxy, benzyloxy, alkyloxycarbonylphenoxy, acyloxyphenoxy), acyloxy (e.g., propionyloxy, benzoyloxy, acetoxy), carbamoyloxy, carboxy, mercapto, alkylthio, acylthio, arylthio (e.g., phenylthio, chlorophenylthio, alkylphenylthio, alkoxyphenylthio, benzylthio, alkyloxycarbonylphenylthio), amino (e.g., amino, mono- and di- C_1–C_3 alkanylamino, methylphenylamino, methylbenzylamino, C_1–C_3 alkanylamido, carbamamido, ureido, guanidino).

"Heteroatom" is a nitrogen, sulfur, or oxygen atom. Groups containing more than one heteroatom may contain different heteroatoms.

"Heterocyclic aliphatic ring" is a saturated or unsaturated ring containing carbon and from 1 to about 4 heteroatoms in the ring, wherein no two heteroatoms are adjacent in the ring and no carbon in the ring that has a heteroatom attached to it also has a hydroxyl, amino, or thiol group attached to it. Heterocyclic aliphatic rings are not aromatic. Heterocyclic aliphatic rings are monocyclic, or are fused or bridged bicyclic ring systems. Monocyclic heterocyclic aliphatic rings contain from about 4 to about 10 member atoms (carbon and heteroatoms), preferably from 4 to 7, and most preferably from 5 to 6 member atoms in the ring. Bicyclic heterocyclic aliphatic rings contain from 8 to 12 member atoms, preferably 9 or 10 member atoms in the ring. Heterocyclic aliphatic rings may be unsubstituted or substituted with from 1 to about 4 substituents on the ring. Preferred heterocyclic aliphatic ring substituents include: halo, cyano, alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof. More preferred substituents include halo and haloalkyl. Preferred heterocyclic aliphatic rings include piperzyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and piperdyl.

"Heteroaromatic ring" is an aromatic ring system containing carbon and from 1 to about 4 heteroatoms in the ring. Heteroaromatic rings are monocyclic or fused bicyclic ring systems. Monocyclic heteroaromatic rings contain from about 5 to about 10 member atoms (carbon and heteroatoms), preferably from 5 to 7, and most preferably from 5 to 6 member atoms in the ring. Bicyclic heteroaromatic rings contain from 8 to 12 member atoms, preferably 9 or 10 member atoms in the ring. Heteroaromatic rings may be unsubstituted or substituted with from 1 to about 4
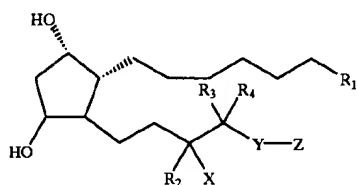
substituents on the ring. Preferred heteroaromatic ring sub-
stituents include: halo, cyano, alkyl, heteroalkyl, haloalkyl,
phenyl, phenoxy or any combination thereof. More preferred
substituents include halo, haloalkyl, and phenyl. Preferred
heteroaromatic rings include thienyl, thiazolo, purinyl,
pyrimidyl, pyridyl, and furanyl. More preferred heteroaro-
matic rings include thienyl, furanyl, and pyridyl. The most
preferred heteroaromatic ring is thienyl.

"Lower alkyl" is an alkyl chain radical comprised of 1 to
6, preferably 1 to 4 carbon atoms.

"Phenyl" is a six-membered monocyclic aromatic ring
which may or may not be substituted with from about 1 to
about 4 substituents. The substituents may be substituted at
the ortho, meta or para position on the phenyl ring, or any
combination thereof. Preferred phenyl substituents include:
halo, cyano, alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy
or any combination thereof. More preferred substituents on
the phenyl ring include halo and haloalkyl. The most pre-
ferred substituent is halo. The preferred substitution pattern
on the phenyl ring is ortho or meta. The most preferred
substitution pattern on the phenyl ring is ortho.

Compounds

The subject invention involves compounds having the
following structure:

In the above structure, R_1 is CO_2H, $C(O)NHOH$, CO_2R_5,
CH_2OH, $S(O)_2R_5$, $C(O)NHR_5$, $C(O)NHS(O)_2R_5$, or tetra-
zole; wherein R_5 is alkyl, heteroalkyl, carbocyclic aliphatic
ring, heterocyclic aliphatic ring, aromatic ring, or heteroaro-
matic ring. Preferred R_5 is CH_3, C_2H_5, C_3H_7. Preferred R_1
is CO_2H, $C(O)NHOH$, CO_2CH_3, $CO_2C_2H_5$, $CO_2C_3H_7$,
$CO_2C_4H_9$, $CO_2C_3H_7O_2$, and $C(O)NHS(O)_2R_5$. More pre-
ferred R_1 is CO_2H, $C(O)NHOH$, CO_2CH_3, and $CO_2C_3H_5$.
Most preferred R_1 is CO_2H and CO_2CH_3.

In the above structure, R_2 is H or lower alkyl. Preferred
R_2 is H and CH_3. Most preferred R_2 is H.

In the above structure, X is NR_6R_7, OR_8, SR_9, $S(O)R_9$, or
$S(O)_2R_9$; wherein R_6,R_7, and R_8 are independently selected
from the group consisting of H, acyl, alkyl, heteroalkyl,
carbocyclic aliphatic ring, heterocyclic aliphatic ring, aro-
matic ring, and heteroaromatic ring; and wherein R_9 is alkyl,
heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic
ring, aromatic ring, or heteroaromatic ring. Preferred R_6 and
R_7 are H, CH_3 and C_2H_5. Preferred R_8 is H, CH_3, C_2H_5 and
C_3H_7. Preferred R_9 is CH_3 and C_2H_5. Preferred X is NR_6R_7
and OR_8. Most preferred X is OH.

In the above structure, R_3 and R_4 are independently
selected from the group consisting of H, CH_3, and C_2H_5.
Preferred R_3 and R_4 are H.

In the above structure, Y is NR_{10}, S, $S(O)$, or $S(O)_2$;
wherein R_{10} is H, acyl, alkyl, heteroalkyl, carbocyclic

aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or
heteroaromatic ring. Preferred R_{10} is H and CH_3. Preferred
Y is NH and S.

In the above structure, Z is carbocyclic aliphatic ring,
heterocyclic aliphatic ring, aromatic ring, or heteroaromatic
ring. Preferred Z is monocyclic carbocyclic aliphatic ring,
monocyclic heterocyclic aliphatic ring, monocyclic aro-
matic ring, and monocyclic heteroaromatic ring. More pre-
ferred Z is monocyclic aromatic ring or monocyclic het-
eroaromatic ring. The most preferred Z is thienyl or phenyl.

The invention also includes optical isomers, diastere-
omers and enantiomers of the above structure. Thus, at all
stereocenters where stereochemistry is not defined (C_{11}, C_{12},
C_{15}, and C_{16}), both epimers are envisioned. Preferred ste-
reochemistry at all such stereocenters of the compounds of
the invention mimic that of naturally occurring PGF_{2a}.

It has been discovered that the novel PGF analogs of the
subject invention are useful for treating bone disorders,
especially those that require a significant increase in bone
mass, bone volume, or bone strength. Surprisingly, the
compounds of the subject invention have been found to
provide the following advantages over known bone disorder
therapies: (1) An increase trabecular number through for-
mation of new trabeculae; (2) An increase in bone mass and
bone volume while maintaining a more normal bone turn-
over rate; and (3) An increase in bone formation at the
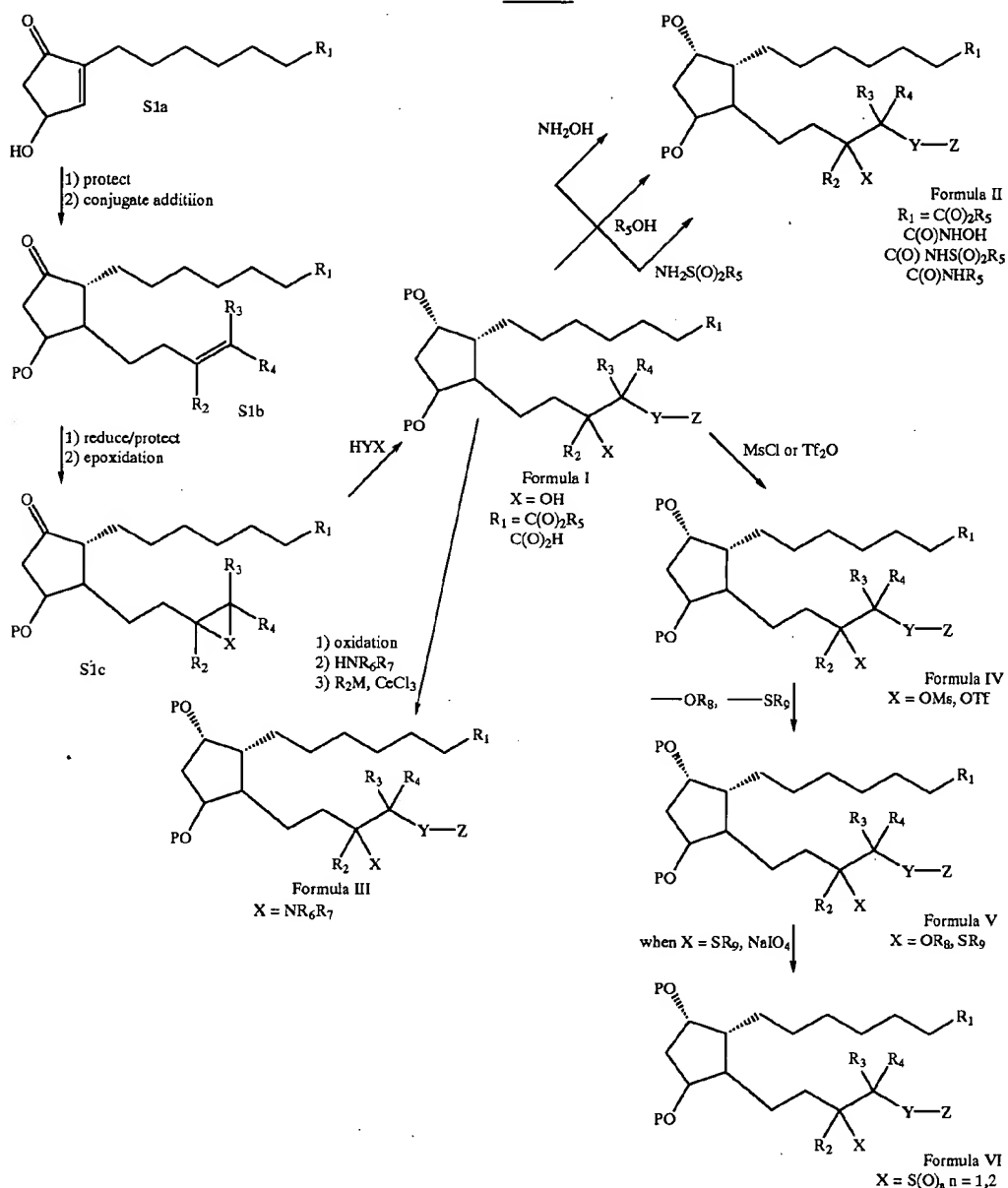endosteal surface without increasing cortical porosity.

In order to determine and assess pharmacological activity,
testing of the subject compounds in animals is carried out
using various assays known to those skilled in the art. For
example, the bone activity of the subject compounds can be
conveniently demonstrated using an assay designed to test
the ability of the subject compounds to increase bone
volume, mass, or density. An example of such assays is the
ovariectomized rat assay.

In the ovariectomized rat assay, six-month old rats are
ovariectomized, aged 2 months, and then dosed once a day
subcutaneously with a test compound. Upon completion of
the study, bone mass and/or density can be measured by dual
energy x-ray absorptometry (DXA) or peripheral quantita-
tive computed tomography (pQCT), or micro computed
tomography (mCT). Alternatively, static and dynamic his-
tomorphometry can be used to measure the increase in bone
volume or formation.

Pharmacological activity for glaucoma can be demon-
strated using assays designed to test the ability of the subject
compounds to decrease intraocular pressure. Examples of
such assays are described in the following reference, incor-
porated herein: C. liijebris, G. Selen, B. Resul, J.
Sternschantz, and U. Hacksell, "Derivatives of 17-Phenyl-
18,19,20-trinorprostaglandin $F_2\alpha$ Isopropyl Ester: Potential
Antiglaucoma Agents", *Journal of Medicinal Chemistry*,
Vol. 38 No. 2 (1995), pp. 289–304.

Compounds useful in the subject invention can be made
using conventional organic syntheses. A particularly pre-
ferred synthesis is the following general reaction scheme:

Scheme 1

In Scheme 1, R_1, R_2, R_3, R_4, X, Y, and Z are as defined above. The Methyl 7-[3-(R)-hydroxy-5-oxo-1-cyclopent-1-yl] heptanoate (S1a) depicted as starting material for Scheme 1 is commercially available (such as from Sumitomo Chemical or Cayman Chemical).

In the above Scheme 1, Methyl 7-[3-(R)-hydroxy-5-oxo-1-cyclopent-1-yl] heptanoate (S1a) is reacted with a silylating agent and base in a solvent that will allow the silylation to proceed. Preferred silylating agents include tert-butyldimethylsilyl chloride and tert-butyldimethylsilyl trifluoromethanesulphonate. The most preferred silylating agent is tert-butyidimethylsilyl trifluoromethanesulphonate. Preferred bases include triethylamine, trimethylamine, and 2,6-lutidine. More preferred bases include triethylamine and 2,6-lutidine. The most preferred base is 2,6-lutidine. Preferred solvents include halocarbon solvents with dichloromethane being the most preferred solvent. The reaction is allowed to proceed at a temperature preferably between –100° C. and 100° C., more preferably between –80° C. and 80° C., and most preferably between –70° C. and 23° C.

The resulting silylated compound is isolated by methods known to those of ordinary skill in the art. Such methods include, but are not limited to, extraction, solvent evaporation, distillation, and crystallization. Preferably, the silyl ether is purified after isolation by distillation under vacuum.

The silylated compound is then reacted with the cuprate generated via Grignard formation of the appropriate alkenyl

bromide as disclosed, for example, in the following references: H. O. House et. al., "The Chemistry of Carbanions: A Convenient Precursor for the Generation of Lithium Organocuprates", *J. Orq. Chem.* Vol. 40 (1975) pp. 1460–69 and P. Knochel et. al., "Zinc and Copper Carbenoids as Efficient and Selective a'/d' Multicoupling Reagents", *J. Amer.Chem. Soc.* Vol. 111 (1989) p. 6474–76. Preferred alkenyl bromides include 4-bromo-1-butene, 4-bromo-1-butyne, 4-bromo-2-methyl-1-butene, and 4-bromo-2-ethyl-1-butene. The most preferred alkenyl bromide is 4-bromo-1-butene. Preferred solvents include ethereal solvents, of which diethyl ether and tetrahydrofuran are preferred. The most preferred solvent is tetrahydrofuran. The Grignard reagent is allowed to form at a temperature between 100° C. and 23° C., more preferably between 85° C. and 30° C., and most preferably between 75° C. and 65° C. The reaction time is preferably between 1 hour and 6 hours, with a more preferred reaction time being between 2 hours and 5 hours, and the most preferred reaction time being between 3 hours and 4 hours.

Once the Grignard reagent is formed, the cuprate is generated from the alkenyl magnesium species. The temperature range for cuprate formation is between –100° C. and 0° C. The preferred temperature range is between –80° C. and –20° C. The more preferred temperature range is between –75° C. and –50° C. The preferred reaction time is between 30 minutes and 6 hours. The more preferred reaction time is between 45 minutes and 3 hours. The most preferred reaction time is between 1 hours and 1.5 hours.

The compound depicted as S1b is isolated by methods known to one of ordinary skill in the art. Such methods include, but are not limited to, extraction, solvent evaporation, distillation, and crystallization. Preferably, S1b is purified by flash chromatography on silica gel (Merck, 230–400 mesh) using 10% EtOAc/hexanes as the eluent.

S1b is then reacted with a hydride reducing agent and a polar, protic solvent to give the Cg alcohol. Preferred reducing agents include lithium aluminum hydride, sodium borohydride, and L-selectride. More preferred reducing agents include sodium borohydride, and L-selectride. The most preferred reducing agent is sodium borohydride. Preferred solvents include methanol, ethanol, and butanol. The most preferred solvent is methanol. The reduction is carried out at a temperature between –100° C. and 23° C. The preferred temperature range is between –60° C. and 0° C. The most preferred temperature range is between –45° C. and –20° C.

The resulting alcohol of S1b is isolated by methods known to one of ordinary skill in the art. Such methods include, but are not limited to, extraction, solvent evaporation, distillation, and crystallization. Preferably, the alcohol is purified by flash chromatography on silica gel (Merck, 230–400 mesh) using 20% EtOAc/hexanes as the eluent.

The alcohol can be protected as described previously herein. The protected or unprotected alcohol is then treated with meta-chloroperbenzoic acid in a halocarbon solvent to provide the novel epoxide intermediate depicted as S1c. Preferred halocarbon solvents include dichloromethane, dichloroethane, and chloroform. More preferred halocarbon solvents are dichloromethane and dichloroethane. The most preferred halocarbon solvent is dichloromethane.

The compound depicted as S1c is isolated by methods known to one of ordinary skill in the art. Such methods include, but are not limited to, extraction, solvent evaporation, distillation, and crystallization. Preferably, S1b is purified by flash chromatography on silica gel (Merck, 230–400 mesh) using 20% EtOAc/hexanes as the eluent.

The intermediate epoxide depicted as S1c can be reacted with a variety of oxygen, sulfur and nitrogen containing nucleophiles as disclosed, for example, in J. G. Smith, "Synthetically Useful Reactants of Epoxides", *Synthesis* (1984) p. 629–656, to provide the C_{11}-protected 13,14-dihydro-15-substituted-16-tetranor Prostaglandin F_1 α derivatives of Formula I.

With sulfur nucleophiles, the reaction is carried out preferably at between 150° C. and 0° C., more preferably between 120° C. and 20° C., and most preferably between 80° C. and 50° C. Preferred bases for the reaction include triethylamine, N,N diisopropylethylamine, and trimethylamine. The most preferred base is triethylamine. Preferred solvents for the reaction are aromatic hydrocarbon solvents. Preferred solvents include xylenes, toluene, and benzene. The most preferred solvent is benzene. With nitrogen and oxygen nucleophiles, preferred solvents include ethereal solvents and polar, protic solvents. More preferred ethereal solvents include diethyl ether, dibutyl ether and tetrahydrofuran. The most preferred ethereal solvent is tetrahydrofuran. More preferred polar, protic solvents include ethyl alcohol, methyl alcohol, and tert-butyl alcohol. The most preferred polar, protic solvent is ethyl alcohol.

The ring-opening process with nitrogen and oxygen nucleophiles can be catalyzed with Lewis acids. Preferred Lewis acids include magnesium perchlorate, trimethylsilyl trifluoromethanesulphonate, and trimethylaluminum. The most preferred Lewis acid is magnesium perchlorate. The reaction is carried out at a temperature between 150° C. and 23° C., preferably between 125° C. and 40° C., and more preferably between 100° C. and 75° C.

The resulting compounds can be isolated, but are generally deprotected using techniques known to one of ordinary skill in the art, and isolated as the final 13,14-dihydro-15-substituted-16-tetranor prostaglandin $F_{1α}$ derivative. Compounds depicted by Formula I are exemplified in Examples 2–28.

Compounds depicted by Formula II can be made directly from those described in Formula I by methods known to one of ordinary skill in the art. For example, the condensation of methyl esters of Formula I with amines or hydroxylamine provides compounds depicted by Formula II. Compounds depicted by Formula II are exemplified in Examples 29–32.

Compounds depicted by Formula IIII can be made directly from those described in Formula I by methods known to one of ordinary skill in the art. The appropriately protected derivative from Formula I is oxidized to the ketone following the process described in the following references: A. McKillop and D. W. Young, "Organic Synthesis Using Supported Reagents—Part 1", *Synthesis* (1979) p. 401–22; G. Piancatelli et al., "Pyridium Chlorochromate: A Versatile Oxidation Organic Synthesis", *Synthesis* (1982) p. 245–58; E. J. Corey and J. W. Suggs, "Pyridinium Chlorochromate: An Efficient Reagent for Oxidation of Primary and Secondary Alcohols to Carbonyl Compounds", *Tetrahedron Lett.* Vol. 31 (1975) p. 2647–50; and references cited therein. The ketone is then condensed with N-methylamine to give the imine. Addition of the methylcerium nucleophile (~1.5 equiv.), as described for example in T. Imamoto, et al., "Carbon-Carbon Bond Forming Reactions Using Cerium Metal or Organocerium (III) Reagents", *J. Org. Chem.* Vol. 49 (1984) p. 3904–12; T. Imamoto, et al., "Reactions of Carbonyl Compounds with Grignard Reagents in the Presence of Cerium Chloride", *J. Am. Chem. Soc.* Vol. 111 (1989) p. 4392–98; and references cited therein, gives the aminomethyl derivative of Formula III. Compounds depicted by Formula III are exemplified in Examples 39–42.

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Compounds depicted by Formula IV and Formula V can be made from compounds described in Formula I by activation and subsequent nucleophilic displacement of the appropriately functionalized hydroxyl group. Transformations of this type are described in the following references: E. J. Corey et al., "Simple Stereospecific Routes to 9-epi-Prostaglandin $F_2\alpha$", *J.C.S. Chem. Comm.* (1975) p. 658–9; E. J. Corey et al., "Superoxide ion as a Synthetically Useful Oxygen Nucleophile", *Tetrahedron Lett.* (1975) p. 3183–6; E. J. Corey et al., "Total Synthesis of 5-desoxy Leukotriene D. A New and Useful Equivalent of the 4-Formyl-Trans, Trans-1,3-Butadienyl Anion", *Tetrahedron Lett.* Vol. 23 (1982) p. 3463–66; and references cited therein. Compounds depicted by Formula V are exemplified in Examples 33–36.

Compounds depicted by Formula VI can be made from those described in Formula V (where X is SR_9) by selective oxidation procedures as described, for example, in the following references: E. J. Corey et al., "Pathways for Migration and Cleavage of the S-Peptide Unit of the Leukotrienes", *Tetrahedron Lett.* Vol. 23 (1982) p. 3467–70; *Prostaglandin* Vol. 24 (1982) p. 801; Y. Girard et al., "Synthesis of the Sulfones of Leukotrienes C_4, D_4, and E_4", *Tetrahedron Lett.* Vol. 23 (1982) p. 1023–26; and references cited therein. Compounds depicted by Formula VI are exemplified in Examples 37–38.

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The following non-limiting examples illustrate the compounds, compositions, and uses of the present invention.

Examples Compounds are analyzed using ^1H and ^{13}C NMR, Elemental analysis, mass spectra, high resolution mass spectra and/or IR spectra as appropriate.

Typically, inert solvents are used, preferably in dried form. For example, tetrahydrofuran (THF) is distilled from sodium and benzophenone, diisopropylamine is distilled from calcium hydride and all other solvents are purchased as the appropriate grade. Chromatography is performed on silica gel (70–230 mesh; Aldrich) or (230–400 mesh; Merck) as appropriate. Thin layer chromatography analysis is performed on glass mounted silica gel plates (200–300 mesh; Baker) and visualized using UV, 5% phosphomolybdic acid in EtOH, or ammonium molybdate/cerric sulfate in 10% aqueous H_2SO_4.

Example 1

Preparation of 13,14-dihydro-16-(3-fluorophenylthio) tetranor prostaglandin $F_1\alpha$ (1i), and 13,14-dihydro-15-methyl-16-(3-fluorophenylthio) tetranor prostaglandin $F_1\alpha$ (1j):

13   14

-continued

LiOH, THF/H₂O →

1g, R = H
1h, R = CH3

1g, R = H
1h, R = CH3

a. Methyl 7-(2-oxo-4-(1,1,2,2-tetramethyl-1-silapropoxy) cyclopent-1-enyl) heptanoate 1b: To a solution of Methyl- 7-[3-(R)-hydroxy-5-oxo-1-cyclopenten-1-yl] heptanoate 1a (1 equiv.) in CH₂Cl₂ at −78° C. is added 2,6 Lutidine (1.3 equiv.) dropwise over 15 minutes. The solution is kept at −78° C., and TBDMS Triflate (1.2 equiv.) in CH₂Cl₂ is added dropwise over 15 minutes. The reaction is warmed gradually to room temperature and stirred at room temperature for 15 hours. Aqueous 10% HCl is added and the layers are separated. The water layer is extracted with CH₂Cl₂ and the organic layers are combined. The organic layer is washed with brine, dried (Na₂SO₄) and concentrated. The residue is distilled under vacuum (10 mm Hg) to provide the silyl ether 1b as a yellow liquid.

b. Methyl 7-(5-but-3-enyl-2-hydroxy-4-(1,1,2,2-tetramethyl-1-silapropoxy)cyclopentyl) heptanoate 1c, 1d: To a slurry of Mg⁰ powder (2 equiv.) in THF at room temperature is added one crystal of I₂ and 1-bromobutene (2 equiv.) dropwise over 10 minutes. The reaction proceeds to exotherm as the addition continues. After the addition is complete, the reaction is refluxed for 3 hours and cooled to room temperature. The Grignard is diluted with THF and added via cannula to a 3-necked flask equipped with mechanical stirring and charged with CuBr.DMS (2 equiv.) in a 1:1 solution of THF/DMS at −78° C. After the addition of the Grignard (~20 min), the reaction is stirred for 1 hour at −78° C. The color of the reaction is dark red at this point. A solution of the ketone 1b (1 equiv.) in THF is then added dropwise over 25 minutes. The reaction is stirred at −78° C. for 15 minutes, then allowed to warm slowly to room temperature over 2 hours. The reaction is quenched with aqueous NH₄Cl and the excess DMS is allowed to evaporate overnight. The reaction is partitioned between brine/CH₂Cl₂ and the layers are separated. The aqueous layer is back-extracted with CH₂Cl₂ and the organic layers are combined and dried (Na₂SO₄). The solvent is removed in vacuo and the residue is chromatographed on SiO₂ (10% hexane/ EtOAc) to give the ketone precursor to 1c as a clear oil. The ketone precursor to 1d is prepared in substantially the same manner.

The ketone precursor to 1c (1 equiv.) is dissolved in MeOH and cooled to −40° C. Sodium borohydride (0.9 equiv.) is added portionwise over 10 minutes. After the addition is complete, the reaction is stirred for 13 hours at

−40° C. and then for 12 hours at −78° C. The reaction is quenched with water, partitioned between brine and CH₂Cl₂, and the layers separated. The aqueous layer is back-extracted with CH₂Cl₂ and the organic layers are combined and dried (Na₂SO₄). The solvent is removed in vacuo and the residue chromatographed on SiO₂ (30% EtOAc/ hexanes) to give the alcohol 1c as a colorless oil. Alcohol 1d is prepared in substantially the same manner.

C. Methyl 7-(2-hydroxy-5-(2-(2-oxiranyl)ethyl-4-(1,1,2,2-tetramethyl-1-silapropoxy)cyclopentyl) heptanoate 1e, 1f: The alcohol 1c (1 equiv.) is dissolved in CH₂Cl₂ and cooled to 0° C. Sodium bicarbonate is added, followed by m-CPBA (57%–85% purity) (3 equiv.) portionwise over 15 minutes. After the addition is complete, the reaction is stirred for 20 hours at room temperature. The reaction is poured into water, partitioned between brine and CH₂Cl₂, and the layers are separated. The aqueous layer is back-extracted with CH₂Cl₂ and the organic layers are combined and dried (Na₂SO₄). The solvent is removed in vacuo and the residue is chromatographed on SiO₂ (20% EtOAc/hexanes) to give the epoxide diasteriomers 1e as a colorless oil. Compound 1f is synthesized in substantially the same manner.

d. 13,14-dihydro-16-(3-fluorophenylthio) tetranor prostaglandin F₁α (1g), and 13,14-dihydro-15-methyl-16-(3-fluorophenylthio) tetranor prostaglandin F₁α (1h) methyl esters: In a 5 mL round-bottomed flask, epoxide 1e (1 equiv.) and 100 uL of dry benzene are added. The flask is cooled to 0° C., then is treated with 60 uL of 3-fluoro thiophenol (1.2 eq) and 78 uL of triethyl amine (1.2 eq) as disclosed in J. G. Smith, "Synthetically Useful Reactants of Epoxides", Synthesis (1984) p. 629–656, and references cited therein. The ice bath is removed and the reaction is stirred at room temperature under nitrogen overnight. TLC is used to monitor the reaction. Excess thiophenol is added if necessary. The reaction is quenched with brine and is extracted with methylene chloride. The organic layer is washed three times with 1N HCl, brine, dried over sodium sulfate, and concentrated. Without further purification to this crude reaction mixture, 3 mL of CH₃CN and 0.1 mL of HF/Pyridine (0.1 mmol) are added while the flask is kept at 0° C. After 3 hours at 0° C., the reaction is quenched with saturated NaCl. The aqueous layer is extracted three times with CH₂Cl₂. The organic layers are combined and washed three time with 1N HCl, brine, and dried (Na₂SO₄). After column chromatography,
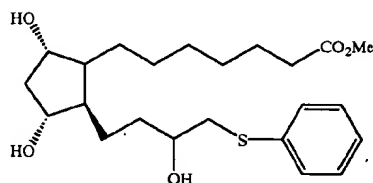
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(7:3, Hexane: Ethyl Acetate) the clear oil 1g is obtained. The ester 1h is prepared in substantially the same manner.

e. 13,14-dihydro-16-(3-fluorophenylthio) tetranor prostaglandin $F_1\alpha$ (1i), and 13,14-dihydro-15-methyl-16-(3-fluorophenylthio) tetranor prostaglandin $F_1\alpha$ (1j): To a 5 ml round-bottomed flask, 50 mg (0.12 mmol) of 13,14-dihydro-16-(3-fluorop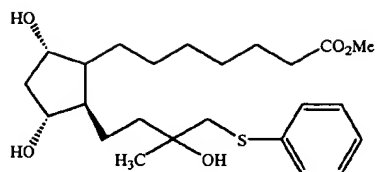henylthio) tetranor Prostaglandin $F_1\alpha$ methyl ester 1 g and 4 mL of THF water solution (3:1, THF:H_2O) are added, and the flask is cooled at 0° C. An excess amount (2.5 equiv.) of lithium hydroxide is added, the ice bath is removed, and the reaction is stirred at room temperature overnight. Methylene chloride and saturated citric acid are added to the reaction mixture, the aqueous layer is washed 3 times with methylene chloride, the organic layers are combined and washed with brine, dried (Na_2SO_4), concentrated in vacuo, and the residue is chromatographed (methylene chloride, methanol, acetic acid, 9.6, 0.4, 0.015), to provide 30 mg of the clear oil 1i. The acid 1j is prepared in substantially the same manner.

Utilizing substantially the method of Example 1 (and using the appropriate thiophenol), the following subject compounds of Examples 2–23 are obtained.

Example 2

13,14-dihydro-16-(phenylthio) tetranor Prostaglandin $F_1\alpha$ methyl ester

Example 3

13,14-dihydro-16-(3-methylphenylthio) tetranor Prostaglandin $F_1\alpha$ methyl ester

Example 4

13,14-dihydro-16-(3-trifluoromethylphenylthio) tetranor Prostaglandin $F_1\alpha$ methyl ester

Example 5

13,14-dihydro-16-(2,3,5,6-tetrafluorophenylthio) tetranor Prostaglandin $F_1\alpha$ methyl ester

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Example 6

13,14-dihydro-16-(2-methylphenylthio) tetranor Prostaglandin $F_1\alpha$ methyl ester

Example 7

13,14-dihydro-16-(4-methylphenylthio) tetranor Prostaglandin $F_1\alpha$ methyl ester

Example 8

13,14-dihydro-16-(2-fluorophenylthio) tetranor Prostaglandin $F_1\alpha$ methyl ester

Example 9

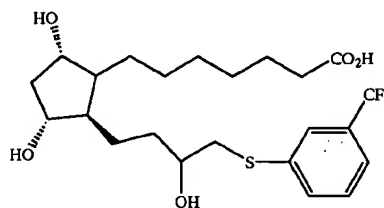13,14-dihydro-15-methyl-16-(phenylthio) tetranor Prostaglandin $F_1\alpha$ methyl ester
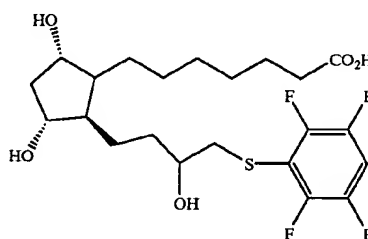
17

Example 10

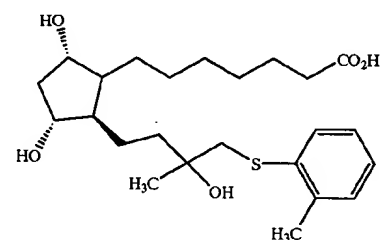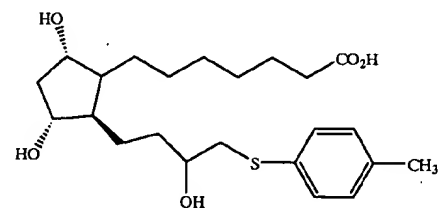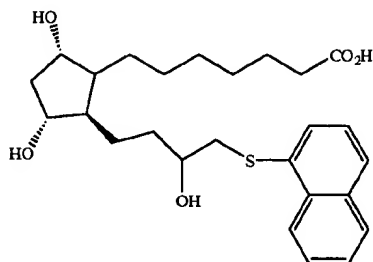13,14-dihydro-15-methyl-16-(2-methylphenylthio) tetranor Prostaglandin $F_1\alpha$ methyl ester

Example 11

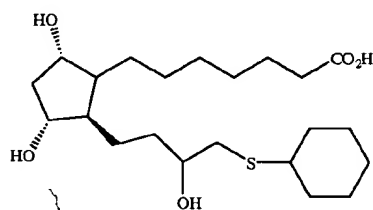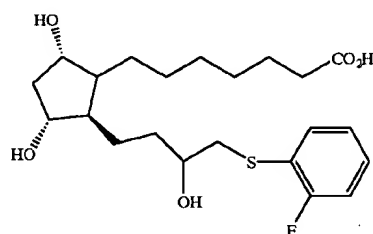13,14-dihydro-16-(2-thienylthio) tetranor prostaglandin $F_1\alpha$ methyl ester

Example 12

13,14-dihydro-16-(phenylthio) tetranor Prostaglandin $F_1\alpha$

Example 13

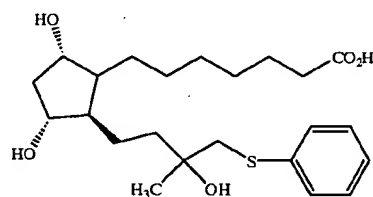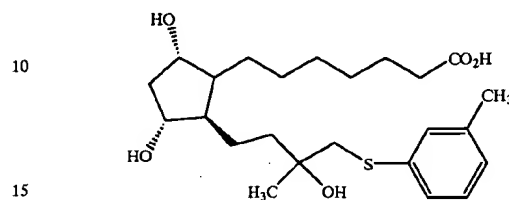13,14-dihydro-16-(3-methylphenylthio) tetranor Prostaglandin $F_1\alpha$

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Example 14

13,14-dihydro-16-(3-trifluoromethylphenylthio) tetranor Prostaglandin $F_1\alpha$

Example 15

13,14-dihydro-16-(2,3,5,6-tetrafluorophenylthio) tetranor Prostaglandin $F_1\alpha$

Example 16

13,14-dihydro-15-methyl-16-(2-methylphenylthio) tetranor Prostaglandin $F_1\alpha$

Example 17

13,14-dihydro-16-(4-methylphenylthio) tetranor Prostaglandin $F_1\alpha$

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Example 18

13,14-dihydro-16-(1-napthylthio) tetranor Prostaglandin $F_1\alpha$

Example 19

13,14-dihydro-16-(cyclohexylthio) tetranor Prostaglandin $F_1\alpha$

Example 20

13,14-dihydro-16-(2-fluorophenylthio) tetranor Prostaglandin $F_1\alpha$

Example 21

13,14-dihydro-15-methyl-16-(phenylthio) tetranor Prostaglandin $F_1\alpha$

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Example 22
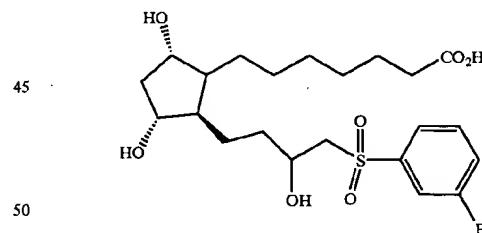
13,14-dihydro-15-methyl-16-(3-methylphenylthio) tetranor Prostaglandin $F_1\alpha$

Example 23

13,14-dihydro-16-(3-fluorophenylsulfonyl) tetranor Prostaglandin $F_1\alpha$:

To a solution of 13,14-dihydro-16-(3-fluorophenylthio) tetranor Prostaglandin $F_1\alpha$ (1 equiv.) in $CHCl_3$ at $-78°$ C. is added peracetic acid (2 equiv.) dropwise. The solution is kept at $-78°$ C. for 1 hour, then it is allowed to warm to $0°$ C. and is kept at $0°$ C. for 1 hour. Saturated NaCl is added and the layers are separated. The water layer is extracted with CH_2Cl_2 and the organic layers are combined. The organic layer is washed with brine, dried (Na_2SO_4) and concentrated. The residue is chromatographed on SiO_2 (96 CH_2Cl_2, 4 MeOH, 0.1 Acetic acid) to give 13,14-dihydro-16-(3-fluorophenylsulfonyl) tetranor Prostaglandin $F_1\alpha$ as a clear oil.

Example 24
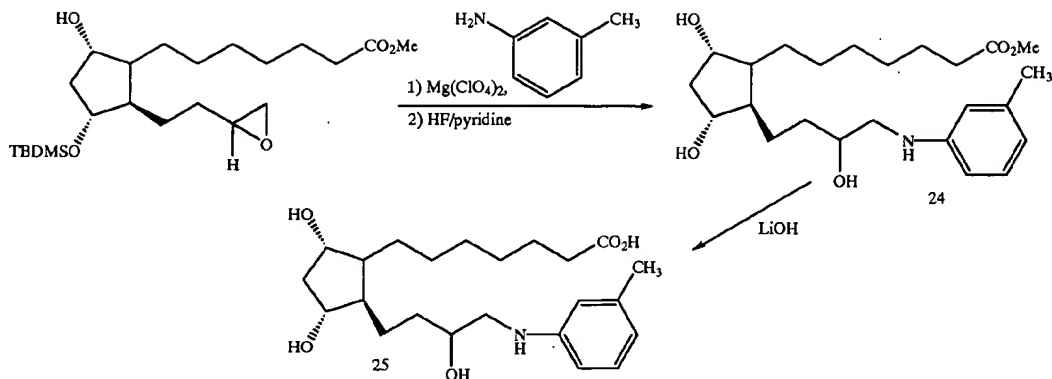
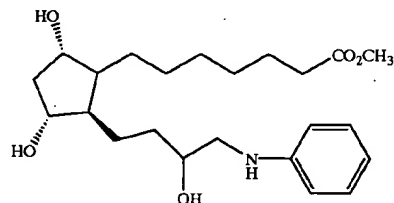Preparation of 13,14-dihydro-16-(3-methylphenylamino) tetranor prostaglandin $F_1\alpha$ methyl ester:

5,977,173

21   **22**

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Example 26

13,14-dihydro-16-(phenylamino) tetranor prostaglandin $F_1\alpha$ methyl ester

Example 27

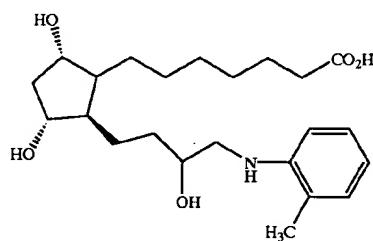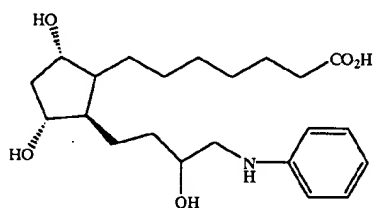13,14-dihydro-16-(2-methylphenylamino) tetranor prostaglandin $F_1\alpha$

Example 28

13,14-dihydro-16-(phenylami no) tetranor prostaglandin $F_1\alpha$

To a 10 mL round-bottomed flask, epoxide 1e (1.26 mmol), m-Toludine (1.5 equiv.), 10 mg of magnesium perchlorate and 2 mL THF are added, after which the reaction is refluxed under nitrogen overnight. The flask is cooled to room temperature and the solvent removed in vacuo. Without further purification of this crude reaction mixture, 3 mL of CH_3CN and 0.5 mL of HFlPyridine (0.5mmol, 0.6 equiv.) are added while the flask is kept at 0° C. After 5 hours at 0° C., the reaction is quenched with saturated NaCl. The aqueous layer is extracted three times with CH_2Cl_2. The organic layers are combined and washed three time with saturated $NaHCO_3$, brine, and dried (Na_2SO_4). After column chromatography (95% CH_2Cl_2, 5% MeOH) 13,14-dihydro-16-(3-methylphenylamino) tetranor prostaglandin $F_1\alpha$ methyl ester is obtained as a clear oil.

Example 25

Preparation of 13,14-dihydro-16-(3-methylphenylamino) tetranor prostaglandin $F_1\alpha$:
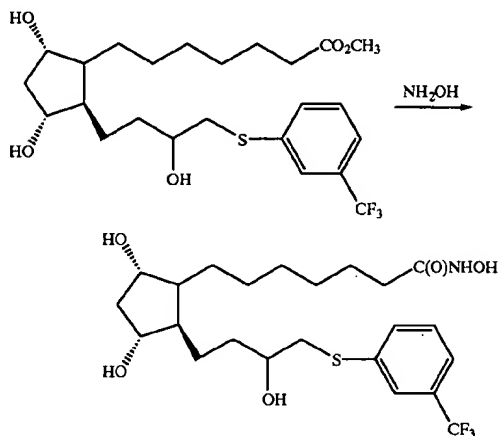
To a 5 ml round-bottomed flask, 13,14-dihydro-16-(3-methylphenylamino) tetranor Prostaglandin $F_1\alpha$ methyl ester (0.15 mmol) and 4 mL of THF water solution (3:1, THF:H_2O) are added. The flask is cooled to 0° C., and excess an amount of lithium hydroxide (2.5 equiv.) is added. The ice bath is removed, and the reaction is stirred at room temperature overnight. Methylene chloride and saturated citric acid are added to the reaction mixture, and the aqueous layer is washed 3 times with methylene chloride. The organic layers are combined and washed with brine, dried (Na_2SO_4), concentrated, and chromatographed (methylene chloride, methanol, acetic acid, 9.6, 0.4, 0.015), to provide 13,14-dihydro-16-(3-methylphenylamino) tetranor prostaglandin $F_1\alpha$ as a clear oil.

Utilizing substantially the method of Examples 24 and 25 (and using the appropriate aniline), the following subject compounds of Examples 26–28 are obtained.

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Example 29

Preparation of 13,14-dihydro-16-(3-trifluoromethylphenylthio) tetranor Prostaglandin $F_1\alpha$ 1-hydroxamic acid:
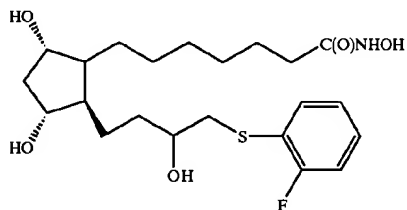

NH$_2$OH →

In a flame-dried 25 mL round-bottomed flask equipped with a magnetic stir bar is placed 13,14-dihydro-16-(3-trifluoromethyphenylthio) tetranor Prostaglandin $F_1\alpha$ methyl ester (Example 4) (1.0 equiv.) in methanol. To this solution is added hydroxylamine in methanol (1.25 equiv.). The solution stirred for 18 hours. The solution is then treated with 1 N hydrochloric acid and extracted with ethyl acetate. The organic layer is washed with brine, dried over anhydrous MgSO$_4$, filtered and concentrated under reduced pressure. The residue is purified by chromatography to give 13,14-dihydro-16-(3-trifluoromethylphenylthio) tetranor Prostaglandin $F_1\alpha$ 1-hydroxamic acid.

Utilizing substantially the method of Example 29 (using the appropriate hydroxylamine or sulfonamide), the following subject compounds of Examples 30–32 are obtained.
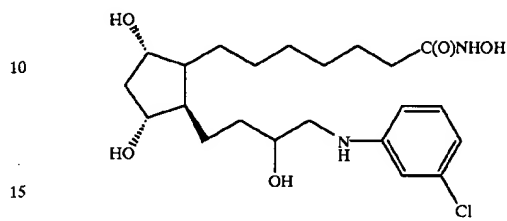
Example 30

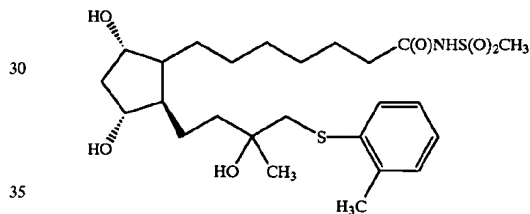13,14-dihydro-16-(2-fluorophenylthio) tetranor Prostaglandin $F_1\alpha$ 1-hydroxamic acid

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Example 31

13,14-dihydro-16-(3-chlorophenylamino) tetranor Prostaglandin $F_1\alpha$ 1-hydroxamic acid
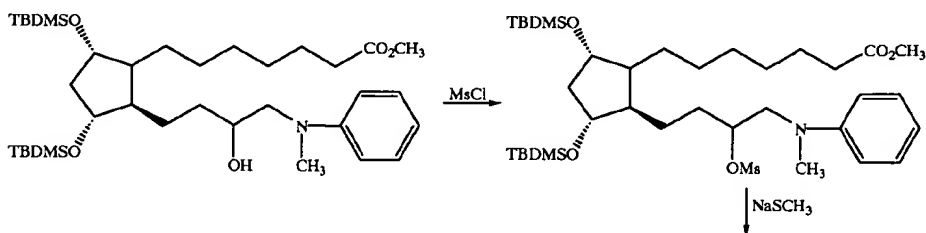

Example 32

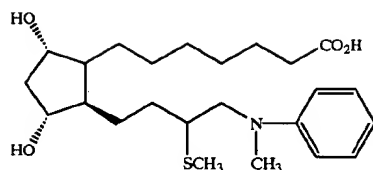13,14-dihydro-15-methyl-16-(2-methylphenylthio) tetranor Prostaglandin $F_1\alpha$ 1-N-methanesulfonamide

Example 33

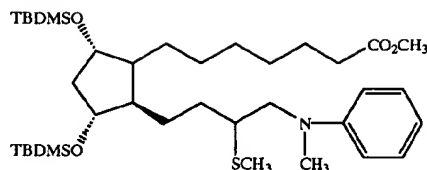Preparation of 13,14-dihydro-15-methylthio-15-dehydroxy-16-(N-methylphenylamino) tetranor Prostaglandin $F_1\alpha$:

MsCl →

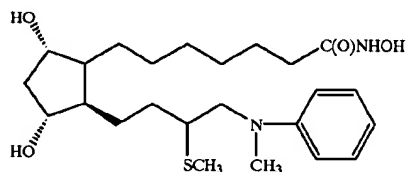NaSCH$_3$ ↓

-continued

→ Example 1

The appropriate bis-silylated compound synthesized in Example 1 is treated with methanesulfonyl chloride (1.2 equiv.) and base (1.2 equiv.) as described in the following references: E. J. Corey et al., "Simple Stereospecific Routes to 9-epi-Prostaglandin $F_2\alpha$", *J.C.S. Chem. Comm.* (1975) p. 658–9; E. J. Corey et al., "Superoxide ion as a Synthetically Useful Oxygen Nucleophile", *Tetrahedron Lett.* (1975) p. 3183–6; and references cited therein, to generate the intermediate mesylate, which is then treated immediately with nucleophiles (sodium thiomethoxide) as described in E. J. Corey et al., "Total Synthesis of 5-desoxy Leukotriene D. A New and Useful Equivalent of the 4-Formyl-Trans,Trans-1, 3-Butadienyl Anion", *Tetrahedron Lett.* Vol. 23 (1982) p. 3463–66, and references cited therein, to give 13,14-dihydro-15-methylthio-15-dehydroxy-16-(N-methylphenylamino) tetranor Prostaglandin $F_1\alpha$ after deprotection as described in Example 1.

Examples 34–36 are prepared using substantially the same procedure as that described in Example 33 (using the appropriate derivative of Formula IV). The skilled artisan may change temperature, pressure, atmosphere, solvents or the order of reactions as appropriate. Additionally, the skilled artisan may use protecting groups to block side reactions or increase yields as appropriate. All such modifications can readily be carried out by the skilled artisan in the art of organic chemistry, and thus are within the scope of the invention.
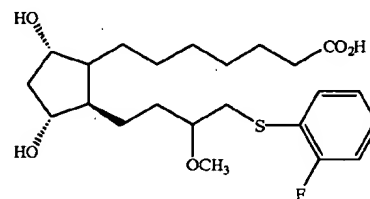
Example 34

13,14-dihydro-15-methylthio-15-dehydroxy-16-(N-methyl-phenylamino) tetranor Prostaglandin $F_1\alpha$ 1-hydroxamic acid
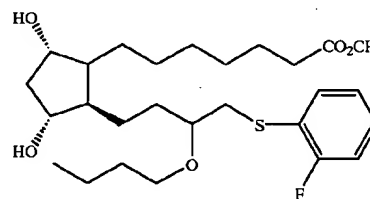

Example 35

13,14-dihydro-15-methoxy-15-dehydroxy-16-(2-fluorophenylthio) tetranor Prostaglandin $F_1\alpha$
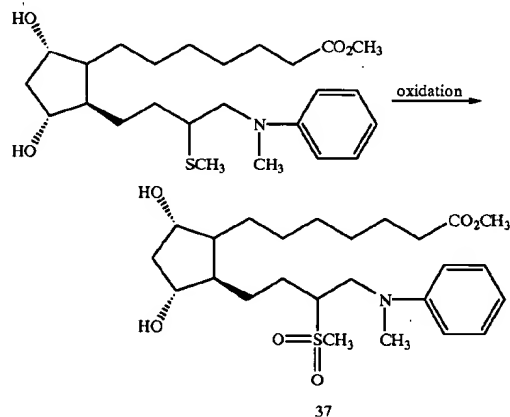

Example 36

13,14-dihydro-15-butoxy-15-dehydroxy-16-(phenylthio) tetranor Prostaglandin $F_1\alpha$ methyl ester

Example 37

Preparation of 13,14-dihydro-15-sulfonylmethyl-15-dehydroxy-16-(N-methylphenylamino) tetranor Prostaglandin $F_1\alpha$ methyl ester:

→ oxidation

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The methyl ester is treated with the appropriate oxidizing agent as described in the following references: E. J. Corey et al., "Total Synthesis of 5-desoxy Leukotriene D. A New and Useful Equivalent of the 4-Formyl-*Trans, Trans*-1,3-Butadienyl Anion", *Tetrahedron Lett.* Vol. 23 (1982) p. 3463–66; *Prostaglandin* Vol. 24 (1982) p. 801; Y. Girard et al., "Synthesis of the Sulfones of Leukotrienes C_4, D_4, and
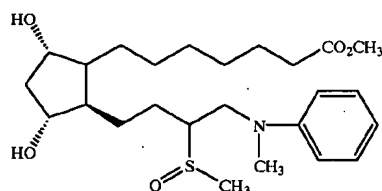
E_4", *Tetrahedron Lett.* Vol. 23 (1982) p. 1023–26; and references cited therein, or as described in Example 23.

Example 38 is prepared using substantially the same procedure as that described in Example 37 (using the appropriate derivative of Formula V). The skilled artisan may change temperature, pressure, atmosphere, solvents or the order of reactions as appropriate. Additionally, the skilled artisan may use protecting groups to block side reactions or increase yields as appropriate. All such modifications can readily be carried out by the skilled artisan in the art of organic chemistry, and thus are within the scope of the invention.
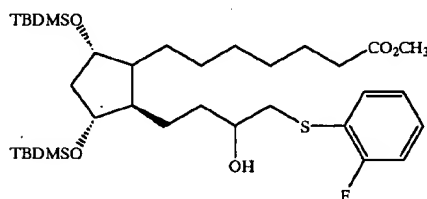
Example 38
13,14-dihydro-15-sulfoxylmethyl-15-dehydroxy-16-(N-methylphenylamino) tetranor Prostaglandin $F_1\alpha$ methyl ester
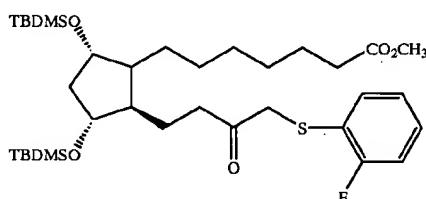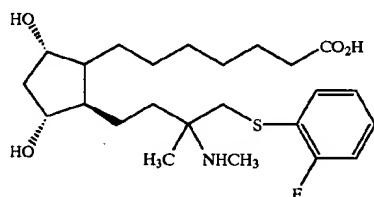

Example 39
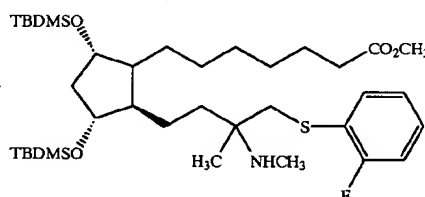Preparation of 13,14-dihydro-15-methyl-15-aminomethyl-16-(2-fluorophenylthio) tetranor Prostaglandin $F_1\alpha$:
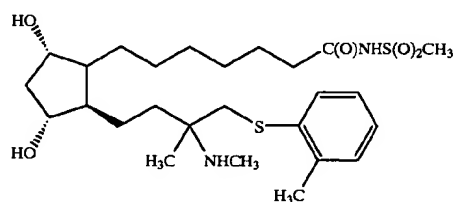

The appropriately protected derivative from Example 8 is oxidized to the ketone as described in the following references: A. McKillop and D. W. Young, "Organic Synthesis Using Supported Reagents—Part 1", *Synthesis* (1979) p. 401–22; E. J. Corey and J. W. Suggs, "Pyridinium Chlorochromate: An Efficient Reagent for Oxidation of Primary and Secondary Alcohols to Carbonyl Compounds", *Tetrahedron Lett.* Vol. 31 (1975) p. 2647–50; and references cited therein, and then condensed with N-methylamine to give the imine. Addition of the methylcerium nucleophile (–1.5 equiv.) (for examples of cerium chloride-mediated nucleophilic addition see: T. Imamoto, et al., "Carbon-Carbon Bond Forming Reactions Using Cerium Metal or Organce-

rium (III) Reagents", *J. Org. Chem.* Vol. 49 (1984) p. 3904–12; T. Imamoto, et al., "Reactions of Carbonyl Compounds with Grignard Reagents in the Presence of Cerium Chloride", *J. Am. Chem. Soc.* Vol. 111 (1989) p. 4392–98; and references cited therein) gives the aminomethyl derivative, which is then transformed as described in Example 1 to give 13,14-dihydro-15-methyl-15-aminomethyl-16-(2-fluorophenylthio) tetranor Prostaglandin $F_1\alpha$.

Examples 40–42 are prepared using substantially the same procedure as that described in Example 39 (using the appropriate derivative of Formula I). The skilled artisan may change temperature, pressure, atmosphere, solvents or the order of reactions as appropriate. Additionally, the skilled artisan may use protecting groups to block side reactions or increase yields as appropriate. All such modifications can readily be carried out by the skilled artisan in the art of organic chemistry, and thus are within the scope of the invention.
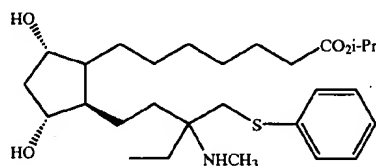
Example 40

13,14-dihydro-15-methyl-15-aminomethyl-16-(2-methylphenylthio) tetranor Prostaglandin $F_1\alpha$ 1-N-methanesulfonamide
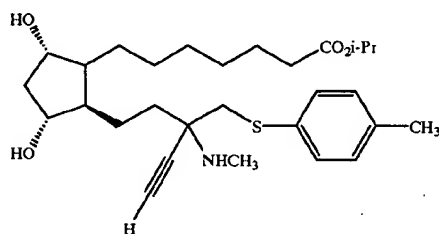
29

Example 41

13,14-dihydro-15-ethyl-15-aminomethyl-16-(phenylthio) tetranor Prostaglandin F$_1\alpha$ isopropyl ester

Example 42

13,14-dihydro-15-ethynyl-15-aminomethyl-16-(4-methylphenylthio) tetranor Prostaglandin F$_1\alpha$ isopropyl ester

Compositions

Compositions of the subject invention comprise a safe and effective amount of the subject compounds, and a pharmaceutically-acceptable carrier. As used herein, "safe and effective amount" means an amount of a compound sufficient to significantly induce a positive modification in the condition to be treated, but low enough to avoid serious side effects (at a reasonable benefit/risk ratio), within the scope of sound medical judgment. A safe and effective amount of a compound will vary with the particular condition being treated, the age and physical condition of the patient being treated, the severity of the condition, the duration of the treatment, the nature of concurrent therapy, the particular pharmaceutically-acceptable carrier utilized, and like factors within the knowledge and expertise of the attending physician.

In addition to the compound, the compositions of the subject invention contain a pharmaceutically-acceptable carrier. The term "pharmaceutically-acceptable carrier", as used herein, means one or more compatible solid or liquid filler diluents or encapsulating substances which are suitable for administration to a subject. The term "compatible", as used herein, means that the components of the composition are capable of being commingled with the compound, and with each other, in a manner such that there is no interaction which would substantially reduce the pharmaceutical efficacy of the composition under ordinary use situations. Pharmaceutically-acceptable carriers must, of course, be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the subject being treated.

Some examples of substances which can serve as pharmaceutically-acceptable carriers or components thereof are sugars, such as lactose, glucose and sucrose; starches, such as cornstarch and potato starch; cellulose and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, cellulose acetate; powdered tragacanth; malt; gelatin; talc; solid lubricants, such as stearic acid, magnesium stearate; calcium sulfate; vegetable oils, such as peanut

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oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma; polyols such as propylene glycol, glycerin, sorbitol, mannitol, and polyethylene glycol; alginic acid; emulsifiers, such as the Tweens®; wetting agents such as sodium lauryl sulfate; coloring agents; flavoring agents, excipients; tableting agents; stabilizers; antioxidants; preservatives; pyrogen-free water; isotonic saline; and phosphate buffer solutions.

The choice of a pharmaceutically-acceptable carrier to be used in conjunction with a compound is basically determined by the way the compound is to be administered. The compounds of the present invention may be administered systemically. Routes of administration include transdermal; oral; parenterally, including subcutaneous or intravenous injection; topical; and/or intranasal.

The appropriate amount of the compound to be used may be determined by routine experimentation with animal models. Such models include, but are not limited to the intact and ovariectomized rat models, the ferret, canine, and non human primate models as well as disuse models.

Preferred unit dosage forms for injection include sterile solutions of water, physiological saline, or mixtures thereof. The pH of said solutions should be adjusted to about 7.4. Suitable carriers for injection or surgical implants include hydrogels, controlled- or sustained release devises, polylactic acid, and collagen matrices.

Suitable pharmaceutically-acceptable carriers for topical application include those suited for use in lotions, creams, gels and the like. If the compound is to be administered perorally, the preferred unit dosage form is tablets, capsules and the like. The pharmaceutically-acceptable carriers suitable for the preparation of unit dosage forms for oral administration are well-known in the art. Their selection will depend on secondary considerations like taste, cost, and shelf stability, which are not critical for the purposes of the subject invention, and can be made without difficulty by those skilled in the art.

Methods of Use

The compounds of the present invention are useful in treating many medical disorders, including for example, ocular disorders, hypertension, fertility control, nasal congestion, neurogenic bladder disorder, gastrointestinal disorders, dermatological disorders, and osteoporosis.

The compounds of the present invention are useful in increasing bone volume and trabecular number through formation of new trabeculae, increasing bone mass while maintaining a normalized bone turnover rate, and formation of bone at the endosteal surface without removing bone from the existing cortex. Thus, these compounds are useful in the treatment and prevention of bone disorders.

The preferred routes of administration for treating bone disorders are transdermal and intranasal. Other preferred routes of administration include rectal, sublingual, and oral.

The dosage range of the compound for systemic administration is from about 0.01 to about 1000 μg/kg body weight, preferably from about 0.1 to about 100 μg/kg per body weight, most preferably from about 1 to about 50 μg/kg body weight per day. The transdermal dosages will be designed to attain similar serum or plasma levels, based upon techniques known to those skilled in the art of pharmacokinetics and transdermal formulations. Plasma levels for systemic administration are expected to be in the range of 0.01 to 100 nanograms/ml, more preferably from 0.05 to 50 ng/ml, and most preferably from 0.1 to 10 ng/ml. While these dosages are based upon a daily administration rate, weekly or monthly accumulated dosages may also be used to calculate the clinical requirements.

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Dosages may be varied based on the patient being treated, the condition being treated, the severity of the condition being treated, the route of administration, etc. to achieve the desired effect.

The compounds of the present invention are also useful in decreasing intraocular pressure. Thus, these compounds are useful in the treatment of glaucoma. The preferred route of administration for treating glaucoma is topically.

Composition and Method Examples

The following non-limiting examples illustrate the subject invention. The following composition and method examples do not limit the invention, but provide guidance to the skilled artisan to prepare and use the compounds, compositions and methods of the invention. In each case other compounds within the invention may be substituted for the example compound shown below with similar results. The skilled practitioner will appreciate that the examples provide guidance and may be varied based on the condition being treated and the patient.

Example A

Pharmaceutical compositions in the form of tablets are prepared by conventional methods, such as mixing and direct compaction, formulated as follows:

Ingredient	Quantity (mg per tablet)
Compound of Example 20	5
Microcrystalline Cellulose	100
Sodium Starch Glycollate	30
Magnesium Stearate	3

When administered orally once daily, the above composition substantially increases bone volume in a patient suffering from osteoporosis.

Example B

Pharmaceutical compositions in liquid form are prepared by conventional methods, formulated as follows:

Ingredient	Quantity
Compound of Example 20	5 mg
Phosphate buffered physiological saline	10 ml
Methyl Paraben	0.05 ml

When 1.0 ml of the above composition is administered subcutaneously once daily, the above composition substantially increases bone volume in a patient suffering from osteoporosis.

Example C

Topical pharmaceutical compositions for lowering intraocular pressure are prepared by conventional methods and formulated as follows:

Ingredient	Amount (wt %)
Compound of Example 42	0.004
Dextran 70	0.1
Hydroxypropyl methylcellulose	0.3
Sodium Chloride	0.77
Potassium chloride	0.12
Disodium EDTA (Edetate disodium)	0.05

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-continued

Ingredient	Amount (wt %)
Benzalkonium chloride	0.01
HCL and/or NaOH	pH 7.2–7.5
Purified water	q.s. to 100%

While particular embodiments of the subject invention have been described, it would be obvious to those skilled in the art that various changes and modifications to the compositions disclosed herein can be made without departing from the spirit and scope of the invention. It is intended to cover, in the appended claims, all such modifications that are within the scope of this invention.

What is claimed is:

1. A compound having the structure:

wherein

(a) R_1 is CO_2H, $C(O)NHOH$, CO_2R_5, CH_2OH, $S(O)_2R_5$, $C(O)NHR_5$, $C(O)NHS(O)_2R_5$, or tetrazole; wherein R_5 is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring;

(b) R_2 is H or lower alkyl;

(c) X is NR_6R_7, OR_8, SR_9, $S(O)R_9$, or $S(O)_2R_9$; wherein R_6, R_7, and R_8 are independently selected from the group consisting of H, acyl, alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring; and wherein R_9 is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring;

(d) R_3 and R_4 are independently selected from the group consisting of H, CH_3, and C_2H_5;

(e) Y is NR_{10}, S, S(O), or $S(O)_2$; wherein R_{10} is H, acyl, alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring;

(f) Z is carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring; and

any optical isomer, diastereomer, enantiomer of the above structure or a pharmaceutically-acceptable salt, or bio-hydrolyzable amide, ester, or imide thereof.

2. The compound according to claim 1 wherein R_1 is selected from the group consisting of CO_2H, $C(O)NHOH$, CO_2CH_3, $CO_2C_2H_5$, $CO_2C_3H_7$, $CO_2C_4H_9$, $CO_2C_3H_7O_2$, and $C(O)NHS(O)_2R_5$.

3. The compound according to claim 2 wherein R_2 is H or CH_3.

4. The compound according to claim 3 wherein X is OR_8 or NR_6R_7.

5. The compound according to claim 4 wherein Z is monocyclic.

6. The compound according to claim 5 wherein Z is aromatic ring or heteroaromatic ring.

7. The compound according to claim 6 wherein Z is thienyl or phenyl.

8. The compound according to claim 7 wherein R_1 is selected from the group consisting of CO_2H, $C(O)NHOH$, CO_2CH_3, and $CO_2C_3H_7$.

9. The compound according to claim 8 wherein X is OH.

10. The compound according to claim 9 wherein Y is S or NH.

11. The compound according to claim 10 wherein Z is substituted, said substituents being independently selected from the group consisting of halo, alkyl, haloalkyl, cyano, nitro, alkoxy, phenyl, and phenoxy.

12. The compound according to claim 10 wherein Z is substituted, said substituents being independently selected from the group consisting of halo, alkyl, cyano, and phenyl.

13. The compound according to claim 10 wherein Z is substituted; said substituents being halo or alkyl.

14. The compound according to claim 13 wherein said compound is selected from the group consisting of:

13,14-dihydro-16-(3-methylphenylthio) tetranor Prostaglandin $F_1\alpha$ methyl ester;

13,14-dihydro-16-(3-methylphenylthio) tetranor Prostaglandin $F_1\alpha$;

13,14-dihydro-16-(3-fluorophenylthio) tetranor Prostaglandin $F_1\alpha$ methyl ester;

13,14-dihydro-16-(3-fluorophenylthio) tetranor Prostaglandin $F_1\alpha$;

13,14-dihydro-16-(2,3,5,6 tetrafluorophenylthio) tetranor Prostaglandin $F_1\alpha$ methyl ester;

13;14-dihydro-16-(2,3,5,6 tetrafluorophenylthio) tetranor Prostaglandin $F_1\alpha$;

13,14-dihydro-16-(2-methylphenylthio) tetranor Prostaglandin $F_1\alpha$ methyl ester;

13,14-dihydro-16-(4-methylphenylthio) tetranor Prostaglandin $F_1\alpha$ methyl ester;

13,14-dihydro-16-(4-methylphenylthio) tetranor Prostaglandin $F_1\alpha$;

13,14-dihydro-16-(2-fluorophenylthio) tetranor Prostaglandin $F_1\alpha$ methyl ester;

13,14-dihydro-16-(2-fluorophenylthio) tetranor Prostaglandin $F_1\alpha$;

13,14-dihydro-15-methyl-16-(3-fluorophenylthio) tetranor Prostaglandin $F_1\alpha$ methyl ester;

13,14-dihydro-15-methyl-16-(3-fluorophenylthio) tetranor Prostaglandin $F_1\alpha$;

13,14-dihydro-15-methyl-16-(2-methylphenylthio) tetranor Prostaglandin $F_1\alpha$ methyl ester;

13,14-dihydro-15-methyl-16-(2-methylphenylthio) tetranor Prostaglandin $F_1\alpha$;

13,14-dihydro-16-(3-fluorophenylsulfonyl) tetranor Prostaglandin $F_1\alpha$;

13,14-dihydro-16-(3-methylphenylamino) tetranor prostaglandin $F_1\alpha$ methyl ester;

13,14-dihydro-16-(3-methylphenylamino) tetranor prostaglandin $F_1\alpha$;

13,14-dihydro-16-(2-methylphenylamino) tetranor prostaglandin $F_1\alpha$ methyl ester;

13,14-dihydro-16-(2-methylphenylamino) tetranor prostaglandin $F_1\alpha$;

13,14-dihydro-16-(2-fluorophenylthio) tetranor prostaglandin $F_1\alpha$ 1-hydroxamic acid;

13,14-dihydro-16-(3-chlorophenylamino) tetranor prostaglandin $F_1\alpha$ 1-hydroxamic acid.

15. The compound according to claim 11 wherein said compound is selected from the group consisting of:

13,14-dihydro-16-(3-trifluoromethylphenylthio) tetranor Prostaglandin $F_1\alpha$ methyl ester;

13,14-dihydro-16-(3-trifluoromethylphenylthio)tetranor Prostaglandin $F_1\alpha$;

13,14-dihydro-16-(3-trifluoromethylphenylthio) tetranor prostaglandin $F_1\alpha$ 1-hydroxamic acid.

16. The compound according to claim 10 wherein said compound is selected from the group consisting of:

13,14-dihydro-16-(phenylthio) tetranor Prostaglandin $F_1\alpha$ methyl ester;

13,14-dihydro-16-(phenylthio) tetranor Prostaglandin $F_1\alpha$;

3,14-dihydro-15-methyl-16-(phenylthio) tetranor Prostaglandin $F_1\alpha$ methyl ester;

13,14-dihydro-15-methyl-16-(phenylthio) tetranor Prostaglandin $F_1\alpha$;

13,14-dihydro-16-(phenylamino) tetranor prostaglandin $F_1\alpha$ methyl ester;

13,14-dihydro-16-(phenylamino) tetranor prostaglandin $F_1\alpha$;

13,14-dihydro-16-(2-thienylthio) tetranor prostaglandin $F_1\alpha$ methyl ester;

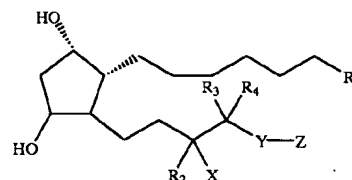13,14-dihydro-16-(2-thienylthio) tetranor prostaglandin $F_1\alpha$.

17. The compound according to claim 8 wherein said compound is selected from the group consisting of:

13,14-dihydro-16-(1-napthylthio) tetranor Prostaglandin $F_1\alpha$ isopropyl ester;

13,14-dihydro-16-(1-napthylthio) tetranor Prostaglandin $F_1\alpha$;

13,14-dihydro-15-butoxy-15-dehydroxy-16-(phenylthio) tetranor prostaglandin $F_1\alpha$ methyl ester.

18. A method of treating a human or other animal subject having a bone disorder, said method comprising administering to said subject a compound according to the structure:

wherein

(a) R_1 is CO_2H, $C(O)NHOH$, CO_2R_5, CH_2OH, $S(O)_2R_5$, $C(O)NHR_5$, $C(O)NHS(O)_2R_5$, or tetrazole; wherein R_5 is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring;

(b) R_2 is H or lower alkyl;

(c) X is NR_6R_7, OR_8, SR_9, $S(O)R_9$, or $S(O)_2R_9$; wherein R_6, R_7, and R_8 are independently selected from the group consisting of H, acyl, alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring; and wherein R_9 is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring;

(d) R_3 and R_4 are independently selected from the group consisting of H, CH_3, and C_2H_5;

(e) Y is NR_{10}, S, S(O), or $S(O)_2$; wherein R_{10} is H, acyl, alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring;

(f) Z is carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring; and

any optical isomer, diastereomer, enantiomer of the above structure or a pharmaceutically-acceptable salt, or bio-hydrolyzable amide, ester, or imide thereof.

19. The method of claim **18** wherein said bone disorder is osteoporosis.

20. The method of claim **19** wherein said bone disorder is post-menopausal.

21. The method of claim **19** wherein said bone disorder is cortico-steroid induced.

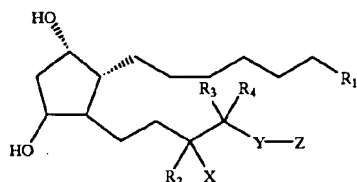22. The method of claim **18** wherein said bone disorder is osteopenia.

23. The method of claim **18** wherein said bone disorder is a bone fracture.

24. The method of claim **18** wherein said compound is administered orally.

25. The method of claim **18** wherein said compound is administered transdermally.

26. The method of claim **18** wherein said compound is administered intranasally.

27. A method of treating glaucoma, said method comprising administering to a human or other animal a safe and effective amount of a compound according to the structure:

wherein

(a) R_1 is CO_2H, $C(O)NHOH$, CO_2R_5, CH_2OH, $S(O)_2R_5$, $C(O)NHR_5$, $C(O)NHS(O)_2R_5$, or tetrazole; wherein R_5 is alkyl, heteroalkyl, carbocyclic aliphatic ring, hetero-cyclic aliphatic ring, aromatic ring, or heteroaromatic ring;

(b) R_2 is H or lower alkyl;

(c) X is NR_6R_7, OR_8, SR_9, $S(O)R_9$, or $S(O)_2R_9$; wherein R_6, R_7, and R_8 are independently selected from the group consisting of H, acyl, alkyl, heteroalkyl, carbocy-clic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring; and wherein R_9 is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic ali-phatic ring, aromatic ring, or heteroaromatic ring;

(d) R_3 and R_4 are independently selected from the group consisting of H, CH_3, and C_2H_5;

(e) Y is NR_{10}, S, S(O), or $S(O)_2$; wherein R_{10} is H, acyl, alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocy-clic aliphatic ring, aromatic ring, or heteroaromatic ring;

(f) Z is carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring; and

any optical isomer, diastereomer, enantiomer of the above structure or a pharmaceutically-acceptable salt, or bio-hydrolyzable amide, ester, or imide thereof.

28. The method of claim **27** wherein said compound is administered topically.

* * * * *

United States Patent [19]

Klimko et al.

[11] **Patent Number:** 5,889,052

[45] **Date of Patent:** *Mar. 30, 1999

[54] **USE OF CLOPROSTENOL AND FLUPROSTENOL ANALOGUES TO TREAT GLAUCOMA AND OCULAR HYPERTENSION**

[75] Inventors: **Peter G. Klimko**, Fort Worth, Tex.; **John E. Bishop**, Groton, Mass.; **Verney L. Sallee**, Burleson; **Paul W. Zinke**, Fort Worth, both of Tex.

[73] Assignee: **Alcon Laboraties, Inc.,** Fort Worth, Tex.

[*] Notice: The term of this patent shall not extend beyond the expiration date of Pat. Nos. 5,510,383, and 5,665,773.

[21] Appl. No.: **917,795**

[22] Filed: **Aug. 21, 1997**

Related U.S. Application Data

[63] Continuation of Ser. No. 769,293, Dec. 18, 1996, Pat. No. 5,665,773, which is a continuation of Ser. No. 280,681, Jul. 26, 1994, abandoned, which is a continuation-in-part of Ser. No. 101,598, Aug. 3, 1993, Pat. No. 5,510,383.

[51] **Int. Cl.^{6}** **A61K 31/557**
[52] **U.S. Cl.** **514/530; 514/573**
[58] **Field of Search** 514/530, 573

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,954,881	5/1976	Bowler	568/645
4,159,343	6/1979	Skuballa et al.	514/548
4,256,745	3/1981	Skuballa et al.	514/239.2
4,321,275	3/1982	Bowler et al.	514/570
4,599,353	7/1986	Bito et al.	514/570
5,173,507	12/1992	DeSantis et al.	514/530
5,288,754	2/1994	Woodward et al.	514/530
5,352,708	10/1994	Woodward et al.	514/729
5,480,900	1/1996	DeSantis et al.	514/392
5,510,383	4/1996	Bishop et al.	514/530
5,565,492	10/1996	DeSantis et al.	514/530
5,605,922	2/1997	DeSantis et al.	514/392
5,665,773	9/1997	Klimko et al.	514/530

FOREIGN PATENT DOCUMENTS

308 135 A2	3/1989	European Pat. Off. .
330 511 A2	8/1989	European Pat. Off. .
364 417 A1	4/1990	European Pat. Off. .
366 279 A2	5/1990	European Pat. Off. .
435 682 A2	7/1991	European Pat. Off. .
603 800 A1	6/1994	European Pat. Off. .
1350971	4/1974	United Kingdom .
14686832	9/1977	United Kingdom .
1553710	10/1979	United Kingdom .
90/02553	3/1990	WIPO .
94/06433	3/1994	WIPO .
94/08585	4/1994	WIPO .

OTHER PUBLICATIONS

Bito et al., "The Ocular Effects of Prostaglandins and the Therapeutic Potential of New $PGF_{2\alpha}$ Analog, PhXA41 (latanoprost), for Glaucoma Management," *J. of Lipid Mediators*, 6:535–543 (1993).

Burke et al., "Prostaglandin $F_{2\alpha}$ Effects on Rabbit IOP Negatively Correlate With Classical $PGF_{2\alpha}$ Receptor Stimulation" *ARVO*, Sarasota, Florida, vol. 29, p. 325, May 1–6, 1988.

Coleman et al., "Prostanoids and their Receptors," *Comprehensive Medicinal Chemistry*, vol. 3, 12.11:643–714.

Narumiya et al., "Structure and Function of Prostanoid Receptors," *J. of Lipid Mediators*, 6:155–161 (1993).

Resul et al., "Phenyl–Substituted Prostaglandins: Potent and Selective Antiglaucoma Agents," *J. Med. Chem.*, 36:243–248 (1993).

Stjernschantz et al., "Phenyl Substituted Prostaglandin Analogs for Glaucoma Treatment," *Drugs of the Future*, 17(8):691–704 (1992).

The Merck Index, 11th Ed., p. 375 (1989).

The Merck Index, 11th Ed., pp. 656–657 (1989).

Woodward et al., "Definition of Prostanoid Receptor Subtypes by Radioligand Binding and the Effects of Selective Agonists on Intraocular Pressure" *Ex. Eye Res.* 55(1):s91 (1992).

Woodward et al., "Intraocular Pressure Effects of Selective Prostanoid Receptor Agonists Involve Different Receptor Subtypes According to Radioligand Binding Studies," *J. of Lipid Mediators*, 6:545–553 (1993).

Zajacz et al., "Effect on Human Eye of Prostaglandin and a Prostaglandin Analogue Used to Induce Abortion,"*IRCS Medical Science: Clinical Medicine: Clinical Pharmacology & Therapeutics: Drug Metabolism & Toxicology: The Eye: Reproduction, Obstetrics & Gynecology*, 4:316 (1976).

Primary Examiner—Richard L. Raymond
Attorney, Agent, or Firm—Barry L. Copeland

[57] **ABSTRACT**

Disclosed is the use of cloprostenol and fluprostenol analogues for the treatment of glaucoma and ocular hypertension. Also disclosed are ophthalmic compositions comprising said compounds.
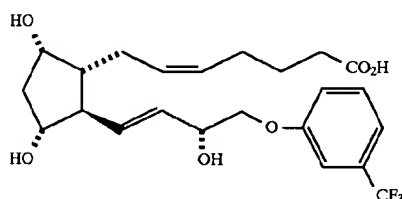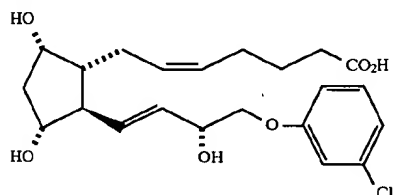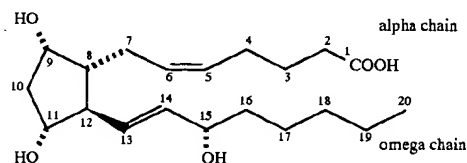
22 Claims, No Drawings

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USE OF CLOPROSTENOL AND FLUPROSTENOL ANALOGUES TO TREAT GLAUCOMA AND OCULAR HYPERTENSION

The present application is a continuation of U.S. patent application Ser. No. 08/769,293, filed Dec. 18, 1996, now U.S. Pat. No. 5,665,773, which is a continuation of U.S. patent application Ser. No. 08/280,681, filed Jul. 26, 1994, now abandoned, which is a continuation-in-part of U.S. patent application Ser. No. 08/101,598 filed Aug. 3, 1993 now U.S. Pat. No. 5,510,383.

BACKGROUND OF THE INVENTION

The present invention relates to the treatment of glaucoma and ocular hypertension. In particular, the present invention relates to the use of cloprostenol and fluprostenol analogues for the treatment of glaucoma and ocular hypertension.

Cloprostenol and fluprostenol, both known compounds, are synthetic analogues of $PGF_{2\alpha}$, a naturally-occurring F-series prostaglandin (PG). Structures for $PGF_{2\alpha}$ (I), cloprostenol (II), and fluprostenol (III), are shown below:

The chemical name for cloprostenol is 16-(3-chlorophenoxy)-17,18,19,20-tetranor $PGF_{2\alpha}$. Monograph No. 2397 (page 375) of *The Merck Index*, 11th Edition (1989) is incorporated herein by reference to the extent that it describes the preparation and known pharmacological profiles of cloprostenol. Fluprostenol has the chemical name 16-(3-trifluoromethylphenoxy)-17,18,19,20-tetranor $PGF_{2\alpha}$. Monograph No. 4121 (pages 656–657) of *The Merck Index*, 11th Edition (1989) is incorporated herein by reference to the extent that it describes the preparation and known pharmacological profiles of fluprostenol. Cloprostenol and fluprostenol are 16-aryloxy PGs and, in addition to the substituted aromatic ring, differ from the natural product $PGF_{2\alpha}$, in that an oxygen atom is embedded within the lower (omega) chain. This oxygen interruption forms an ether functionality.

Naturally-occurring prostaglandins are known to lower intraocular pressure (IOP) after topical ocular instillation, but generally cause inflammation, as well as surface irrita-
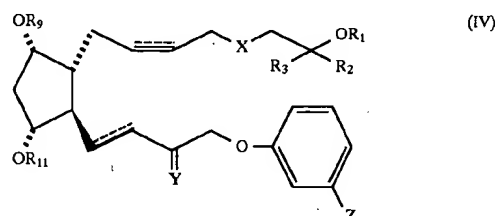
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tion characterized by conjunctival hyperemia and edema. Many synthetic prostaglandins have been observed to lower intraocular pressure, but such compounds also produce the aforementioned side effects which severely restrict clinical utility.

SUMMARY OF THE INVENTION

It has now been unexpectedly found that certain novel cloprostenol and fluprostenol analogues are useful in treating glaucoma and ocular hypertension. In particular, topical application of ophthalmic compositions comprising these novel cloprostenol and fluprostenol analogues result in significant IOP reduction.

DETAILED DESCRIPTION OF THE INVENTION

The compounds useful in the present invention have the following general formula:

wherein:

R_1=H; C_1–C_{12} straight-chain or branched alkyl; C_1–C_{12} straight-chain or branched acyl; C_3–C_8 cycloalkyl; or a cationic salt moiety;

R_2, R_3 =H, or C_1–C_5 straight-chain or branched alkyl; or R_2 and R_3 taken together may represent O;

X=O, S, or CH_2;

- - - represents any combination of a single bond, or a cis or trans double bond for the alpha (upper) chain; and a single bond or trans double bond for the omega (lower) chain;

R_9=H, C_1–C_{10} straight-chain or branched alkyl, or C_1–C_{10} straight-chain or branched acyl;

R_{11} =H, C_1–C_{10} straight-chain or branched alkyl, or C_1–C_{10} straight-chain or branched acyl;

Y=O; or H and OR_{15} in either configuration wherein R_{15}=H. C_1–C_{10} straight-chain or branched alkyl, or C_1–C_{10} straight-chain or branched acyl; and

Z=Cl or CF_3;

with the proviso that when R_2 and R_3 taken together represent O, then $R_1 \neq C_1$–C_{12} straight-chain or branched acyl; and when R_2 =R_3 =H, then $R_1 \neq$ a cationic salt moiety.

As used herein, the term "cationic salt moiety" includes alkali and alkaline earth metal salts as well as ammonium salts.

Preferred compounds include the 3-oxa form of cloprostenol isopropyl ester (Table, 1, compound 5), 13,14-dihydrofluprostenol isopropyl ester (compound 6), cloprostenol-1-ol (compound 7), and 13,14-dihydrocloprostenol-1-ol pivaloate (compound 8).

The compounds of formula (IV) are useful in lowering intraocular pressure and thus are useful in the treatment of glaucoma. The preferred route of administration is topical. The dosage range for topical administration is generally between about 0.01 and about 1000 micrograms per eye (μg/eye), preferably between about 0.1 and about 100

μg/eye, and most preferably between about 1 and 10 μg/eye. The compounds of the present invention can be administered as solutions, suspensions, or emulsions (dispersions) in a suitable ophthalmic vehicle.

In forming compositions for topical administration, the compounds of the present invention are generally formulated as between about 0.00003 to about 3 percent by weight (wt %) solutions in water at a pH between 4.5 to 8.0. The compounds are preferably formulated as between about 0.0003 to about 0.3 wt % and, most preferably, between about 0.003 and about 0.03 wt %. While the precise regimen is left to the discretion of the clinician, it is recommended that the resulting solution be topically applied by placing one drop in each eye one or two times a day.

Other ingredients which may be desirable to use in the ophthalmic preparations of the present invention include preservatives, co-solvents and viscosity building agents.

Antimicrobial Preservatives:

Ophthalmic products are typically packaged in multidose form, which generally require the addition of preservatives to prevent microbial contamination during use. Suitable preservatives include: benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, sorbic acid, ONAMER M®, or other agents known to those skilled in the art. Such preservatives are typically employed at a concentration between about 0.001% and about 1.0% by weight.

Co-Solvents:

Prostaglandins, and particularly ester derivatives, typically have limited solubility in water and therefore may require a surfactant or other appropriate co-solvent in the composition. Such co-solvents include: Polysorbate 20, 60 and 80; Pluronic F-68, F-84 and P-103; Tyloxapol®; Cremophor® EL; sodium dodecyl sulfate; glycerol; PEG 400; propylene glycol; cyclodextrins; or other agents known to those skilled in the art. Such co-solvents are typically employed at a concentration between about 0.01% and about 2% by weight.

Viscosity Agents:

Viscosity greater than that of simple aqueous solutions may be desirable to increase ocular absorption of the active compound, to decrease variability in dispensing the formulations, to decrease physical separation of components of a suspension or emulsion of formulation and/or otherwise to improve the ophthalmic formulation. Such viscosity building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxy propyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxy propyl cellulose or other agents known to those skilled in the art. Such agents are typically employed at a concentration between about 0.01% and about 2% by weight.

The following Examples 1–4 describe the synthesis of compounds 5–8 (Table 1). These syntheses are representative in nature and are not intended to be limiting. Other compounds of formula (IV) may be prepared using analogous techniques known to those skilled in the art.
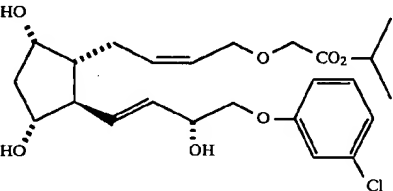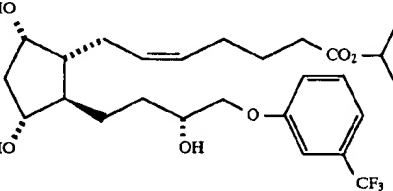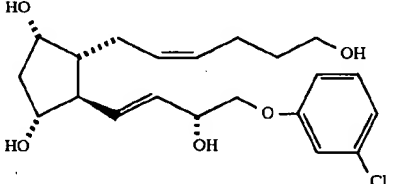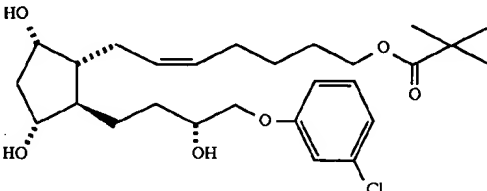
TABLE 1

COMPOUND NAME	COMPOUND STRUCTURE
5 3-oxacloprostenol isopropyl ester	
6 13,14-dihydrofluprostenol isopropyl ester	
7 cloprostenol-1-ol	

TABLE 1-continued

COMPOUND NAME	COMPOUND STRUCTURE
8 13,14-dihydrocloprostenol-1-ol pivaloate	

In the examples below, the following standard abbreviations are used: g=grams (mg=milligrams); mol=moles (mmol=millimoles); mol %=mole percent; mL=milliliters; mm Hg=millimeters of mercury; mp=melting point; bp=boiling point; h=hours; and min=minutes. In addition,

"NMR" refers to nuclear magnetic resonance spectroscopy and "Cl MS" refers to chemical ionization mass spectrometry.

EXAMPLE 1: Synthesis of 3-Oxacloprostenol (5)

-continued

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$(CF_3CH_2O)P(O)CH_2CO_2Me$

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-continued

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A: Ethyl (3-chlorophenoxy)acetate (10)

Acetone (320 ml), 75 g (450 mmol) of ethyl bromoacetate, and 40.0 g (310 mmol) of 3-chlorophenol were mixed together, then 69.8 g (505 mmol) of potassium carbonate was added. The mixture was mechanically stirred and heated to reflux for 4 h, and after cooling to room temperature, was poured into 350 mL of ethyl acetate. To this was then cautiously added 400 mL of 1M HCl, taking care to avoid excess foaming. The layers were separated and the aqueous layer was extracted with portions of ethyl acetate (3×200 mL). The combined organic layers were dried over MgSO$_4$, filtered, concentrated, and the resulting solid was recrystallized from hexane to afford 58 g (87%) of 10 as a white solid, m.p.=39°–40° C. ^{1}H NMR δ 7.20–7.08 (m, 1 H), 6.95–6.82 (m, 2 H), 6.75–6.70 (m, 1 H), 4.53 (s, 2 H), 4.21 (q, J=7.2 Hz, 2 H), 1.23 (t, J=7.2 Hz, 3 H).
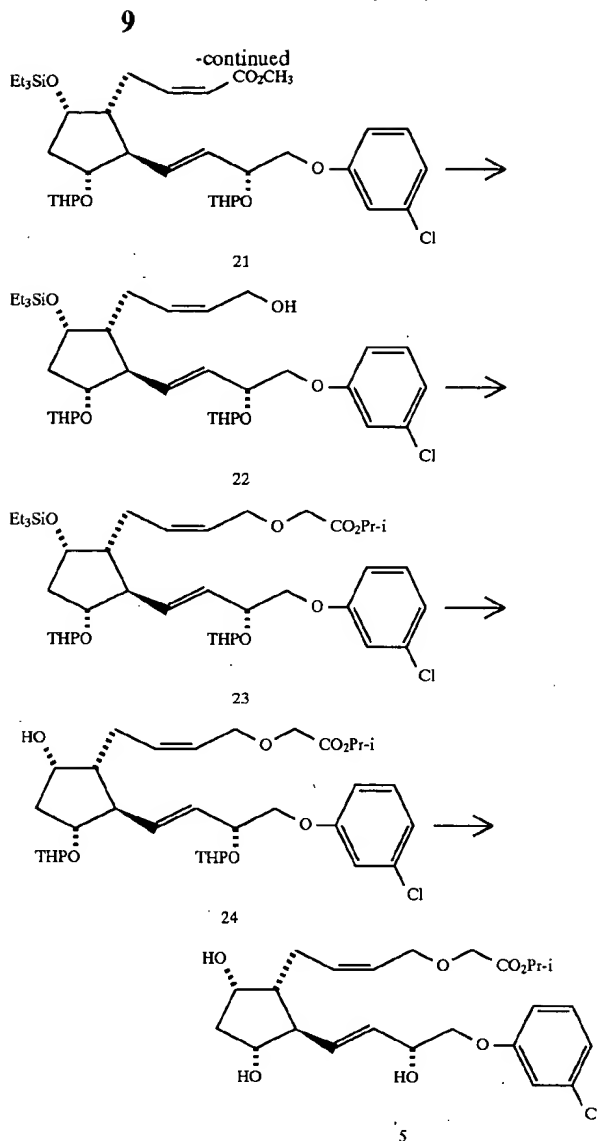
B: Dimethyl [3-(3-chlorophenoxy)-2-oxoprop-1 -yl] phosphonate (11)

To 20.6 g (166 mmol, 238 mol %) of dimethyl methylphosphonate in 110 mL of THF at –78° C. was added

dropwise 65 mL (162 mmol, 232 mol %) of a 2.5M solution of n-BuLi in hexanes. After addition was complete, the mixture was stirred for an additional 1 h, after which 15.0 g (69.9 mmol) of aryloxyester 10 in 40 mL of THF was added dropwise. The reaction was stirred for 1 h and then quenched by the addition of 100 mL of saturated NH$_4$Cl. The mixture was poured into 200 mL of a 1/1 mixture of saturated NaCl/ethyl acetate, layers were separated, and the aqueous layer was further extracted with ethyl acetate (2×100 mL). Combined organic layers were dried over MgSO$_4$, filtered, and concentrated, to afford 20.5 g (100%) of 11 as a viscous oil. ^{1}H NMR δ 7.22 (t, J=8.1 Hz, 1 H), 7.05–6.90 (m, 2 H), 6.85–6.78 (m, 1 H), 4.72 (s, 2 H), 3.84 (s, 3 H), 3.78 (s, 3 H), 3.27 (d, J=22.8 Hz, 2 H).

C: (3aR, 4R, 5R, 6aS)-5-(Benzoyloxy)-4-[(E)-4-(3-chlorophenoxy)-3-oxo-1-butenyl]hexahydro-2H-cyclopenta[b]furan-2-one (13)

Phosphonate 11 (20.5 g, 70.0 mmol), 2.6 g (62 mmol) of LiCl, and 200 mL of THF were mixed together at 0° C. and 6.10 g (60.4 mmol) of NEt$_3$ was added. Aldehyde 12 (14.0

g, 51.1 mmol) dissolved in 50 mL of CH_2Cl_2 was then added dropwise. After 1 h, the reaction was poured into 200 mL of a 1/1 mixture of saturated NH_4Cl/ethyl acetate, the layers were separated, and the aqueous layer was extracted with ethyl acetate (2×100 mL). Combined organic layers were dried over $MgSO_4$, filtered, concentrated, and the residue was chromatographed on silica gel eluting with ethyl acetate/hexanes, 3/2, to afford 16.2 g (72%) of 13 as a white crystalline solid, m.p.=101.0°–102.00° C. ^1H NMR δ 8.0–7.9 (m, 2 H), 7.62–7.52 (m, 1 H), 7.50–7.38 (m, 2 H), 7.18 (t, J=8.2 Hz, 1 H), 7.0–6.82 (m, 3 H), 6.75–6.70 (m, 1 H), 6.54 (d, J=15.1 Hz, 1 H), 5.32 (q, J=6.2 Hz, 1 H), 5.12–5.05 (m, 1 H), 4.66 (s, 2 H), 3.0–2.8 (m, 3 H), 2.7–2.2 (m, 3 H).

D: (3aR, 4R, 5R, 6aS)-5-(Benzoyloxy)-4-[(E)-(3R)-4-(3-chlorophenoxy)-3-hydroxy-1 -butenyl]-hexahydro-2H-cyclopenta[b]furan-2-one (14)

To a solution of 9.70 g (22.0 mmol) of enone 13 in 60 mL of THF at –23° C. was added dropwise a solution of 11.1 g (34.6 mmol) of (-)-B-chlorodiisopino-campheylborane in 30 mL of THF. After 4 h, the reaction was quenched by the dropwise addition of 5 mL of methanol and then warmed to room temperature. After pouring into 200 mL of a 2/1 mixture of ethyl acetate/saturated NH_4Cl, the layers were separated, and the aqueous phase was extracted with ethyl acetate (2×100 mL). Combined organic layers were dried over $MgSO_4$, filtered, concentrated, and the residue was chromatographed on silica gel eluting with ethyl acetate/ hexanes, 3/2, to afford 4.7 g (48%) of 14 as a white solid, m.p. 101.0°–102.5° C. ^1H NMR δ 8.05–7.95 (m, 2 H), 7.62–7.40 (m, 3 H), 7.18 (t, J=8.0 Hz, 1 H), 7.0–6.92 (m, 1 H), 6.85 (t, J=2.1 Hz, 1 H), 6.77–6.70 (m, 1 H), 5.85 (d of d, J=6.2, 15.5 Hz, 1 H), 5.72 (d of d, J=4.5, 15.5 Hz, 1 H), 5.30 (q, J=5.8 Hz, 1 H), 5.12–5.04 (m, 1 H), 4.58–4.48 (m, 1 H), 3.92 (d of d, J=3.5, 9.3 Hz, 1 H), 3.80 (d of d, J=7.3, 9.4 Hz, 1 H), 2.9–2.2 (m, 8 H).

E: (3aR, 4R, 5R, 6aS)-4-[(E)-(3R)-4-(3-Chlorophenoxy)-3-(tetrahydropyran-2-yloxy)-1-butenyl]-5-(tetrahydropyran-2-yloxy)-hexahydro-2H-cyclopenta[b]furan-2-one (16)

To a mixture of 5.1 g (11.5 mmol) of 14 in 200 mL of methanol was added 1.7 g (12 mmol) of K_2CO_3. After 1 h, the mixture was poured into 100 mL of 0.5M HCl and extracted with ethyl acetate (3×100 mL). The combined organic layers were washed successively with water (2×100 mL) and saturated NaCl (2×100 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to afford 4.85 g of crude diol 15, which was used in the next step without further purification.

To a mixture of 4.85 9 of crude 15 and 2.4 g (28 mmol) of 3,4-dihydro-2H-pyran in 75 mL of CH_2Cl_2 at 0° C. was added 370 mg (1.9 mmol) of p-toluenesulfonic acid monohydrate. After stirring for 45 min, the reaction was poured into 40 mL of saturated $NaHCO_3$, layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2×40 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed on silica gel eluting with 40% ethyl acetate in hexanes, to afford 6.0 g (100%) of 16 as an oil. ^1H NMR ($CDCl_3$) δ (characteristic peaks only) 7.25–7.14 (m, 1 H), 6.95–6.87 (m, 2 H), 6.83–6.72 (m, 1 H), 5.8–5.4 (m, 4 H), 5.1–4.8 (m, 2 H).

F: (13E)-(9S, 11R, 15R)-11,15-Bis(tetrahydropyran-2-yloxy)-16-(3-chlorophenoxy)-2,3,4.5,6,17,18,19,20-nonanor-9-triethylsilyloxy-13-prostenol Triethylsilyl Ether (18)

To a suspension of 400 mg (10.5 mmol) of lithium aluminum hydride in 20 mL of THF at 0° C. was added dropwise a solution of 4.5 g (8.8 mmol) of lactone 16 in 20 mL of THF. After 1 h at 0° C. the mixture was cautiously poured into 100 mL of a 1/1 mixture of ice-cold saturated NH_4Cl/ethyl acetate. The layers were separated, and the aqueous layer was extracted with ethyl acetate (2×50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford 4.5 g (100%) of diol 17 which was used in the next step without further purification.

Triethylsilyl chloride (3.0 g, 20 mmol) was added to a mixture of 4.5 g (8.8 mmol) of crude 17, 40 mL of DMF, 1.85 g (27.0 mmol) of imidazole, and 310 mg (2.5 mmol) of 4-(dimethylamino)pyridine. After 2 h, the reaction was poured into 100 mL of a 1/1 mixture of ethyl acetate/ saturated NH_4Cl, layers were separated, and the aqueous layer was extracted with ethyl acetate (2×25 mL). The combined organic layers were washed with water (3×25 mL), dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel eluting with 20% ethyl acetate in hexane to afford 5.2 g (80%) of 18. ^1H NMR ($CDCl_3$) δ (characteristic peaks only) 7.22–7.12 (m, 1 H), 6.95–6.88 (m, 2 H), 6.83–6.71 (m, 1 H), 5.8–5.4 (m, 4 H), 5.1–4.8 (m, 2 H), 1.0–0.85 (m, 18 H), 0.7–0.5 (m, 12 H).

G: (13E)-(9S, 11R, 15R)-11,15-Bis(tetrahydropyran-2-yloxy)-16-(3-chlorophenoxy)-2,3,4,5,6,17,18,19,20-nonanor-9-triethylsilyloxy-13-prostenal (19)

To a mixture of 1.6 g (12.6 mmol) of oxalyl chloride and 15 mL of CH_2Cl_2 at –78° C. was added dropwise a solution of 1.54 g (19.7 mmol) of DMSO in 2 mL of CH_2Cl_2. After 10 min, 4.6 g (6.2 mmol) of bissilane 18 in 8 mL of CH_2Cl_2 was added dropwise. After 95 min, 3.0 g (30 mmol) of NEt_3 was added. The mixture was then warmed to room temperature and poured into 70 mL of saturated NH_4Cl. The solution was extracted with of CH_2Cl_2 (3×70 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed on silica gel eluting with 20% ethyl acetate in hexane to afford 2.06 g (53%) of 19 as well as 1.5 g (26%) recovered 18. ^1H NMR ($CDCl_3$) δ (characteristic peaks only) 9.78 (t, J=1.4 Hz, 1 H), 7.22–7.12 (m, 1 H), 6.95–6.88 (m, 2 H), 6.83–6.71 (m, 1 H), 5.8–5.4 (m, 4 H) 5.1–4.8 (m, 2 H), 1.0–0.85 (m, 18 H), 0.7–0.5 (m, 12 H).

H: (5Z, 13E)-(9S, 11R, 15R)-11,15-Bis(tetrahydropyran-2-yloxy)-16-(3-chlorophenoxy)-2,3,4,17,18,19,20-heptanor-9-triethylsilyloxy-5,13-prostadienoic Acid Methyl Ester (21)

To a solution of 1.35 g (4.24 mmol) of phosphonate 20 and 2.60 g (9.84 mmol) of 18-crown-6 in 20 mL of THF at –78° C. was added dropwise 6.9 mL (3.45 mmol) of a 0.5M solution of potassium hexamethyldisilazane in toluene. After stirring for 15 min, a solution of 1.65 g (2.64 mmol) of aldehyde 19 in 20 mL of THF was added dropwise. One hour later, the mixture was poured into 100 mL of saturated NH_4Cl/ethyl acetate, 1/1, layers were separated, and the aqueous layer was extracted with ethyl acetate (3×30 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and the residue was chromatographed on silica gel eluting with 20% ethyl acetate in hexane to afford 1.135 g (63%) of 21. ^1H NMR ($CDCl_3$) δ (characteristic peaks only) 7.22–7.11 (m, 1 H), 6.97–6.86 (m, 2 H), 6.85–6.75 (m, 1 H), 6.4–6.2 (m, 1 H), 5.8–5.32 (m, 3 H), 3.66 (s, 3 H).

I: (5Z, 13E)-(9S, 11R, 15R)-11,15-Bis(tetrahydropyran-2-yloxy)-16-(3-chlorophenoxy)-2,3,4,17,18,19,20-heptanor-9-triethylsilyloxy-5,13-prostadien-1-ol (22)

To a solution of 850 mg (1.25 mmol) of ester 21 in 10 mL of THF at 0° C. was added 2.4 mL (3.6 mmol) of a 1.5M solution of diisobutylaluminum hydride in toluene. After 1 h, the mixture was poured into 20 mL of saturated NH_4Cl and was extracted with ethyl acetate (3×20 mL). Combined organic layers were dried over $MgSO_4$, filtered, and concentrated down to 800 mg (98%) of 22 as an oil. ^1H NMR ($CDCl_3$) δ (characteristic peaks only) 7.25–7.15 (m, 1 H), 6.97–6.90 (m, 2 H), 6.86–6.75 (m, 1 H), 5.81–5.41 (m, 4 H).

J: (5Z, 13E)-(9S, 11R, 15R)-11,15-Bis(tetrahydropyran-2-yloxy)-16-(3-chlorophenoxy)-3-oxa-17,18,19,20-tetranor-9-triethylsilyloxy-5,13-grostadienoic Acid Isopropyl Ester (23)

To a solution of 415 mg (6.37 mmol) of alcohol 22 in 4 mL of THF at −78° C. was added dropwise 0.35 mL (0.87 mol) of a 2.5M solution of n-BuLi in hexane. After 15 min, this solution was transferred via syringe to a −78° C. solution of 195 mg (1.08 mmol) of isopropyl bromoacetate in 2 mL of THF. The mixture was kept at −78° C. for 40 min, warmed to room temperature overnight, and then poured into 20 mL of a 1/1 mixture of saturated NH_4Cl/ethyl acetate. Layers were separated, and the aqueous layer was extracted with ethyl acetate (2×10 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and the residue was chromatographed on silica gel (20% ethyl acetate in hexane) to afford 242 mg (53%) of 23 as an oil. ^1H NMR ($CDCl_3$) δ (characteristic peaks only) 7.24–7.15 (m, 1 H), 6.97–6.90 (m, 2 H), 6.86–6.75 (m, 1 H), 5.81–5.41 (m, 4 H), 1.57 (d, J=5.7 Hz, 6 H).
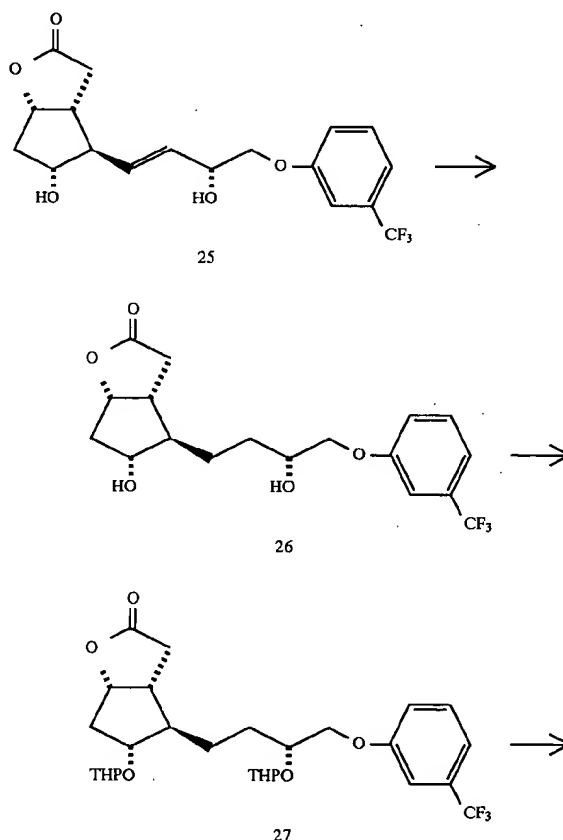
K: (5Z, 13E)-(9S, 11R, 15R)-16-(3-Chlorophenoxy)-3-oxa-17,18,19,20-tetranor-9,11,15-trihydroxy-5,13-prostadienoic Acid Isopropyl Ester (5)

To a solution of 230 mg (0.32 mmol) of silane 23 in 5 mL of THF at room temperature was added 0.33 mL (0.33 mmol) of a 1M solution of Bu_4NF in THF. After 20 min, the reaction was poured into 4 mL of saturated NH_4Cl and was extracted with ethyl acetate (4×5 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and the residue was chromatographed on silica gel (ethyl acetate/hexane, 1/1), to afford 126 mg (65%) of desilylated compound 24.
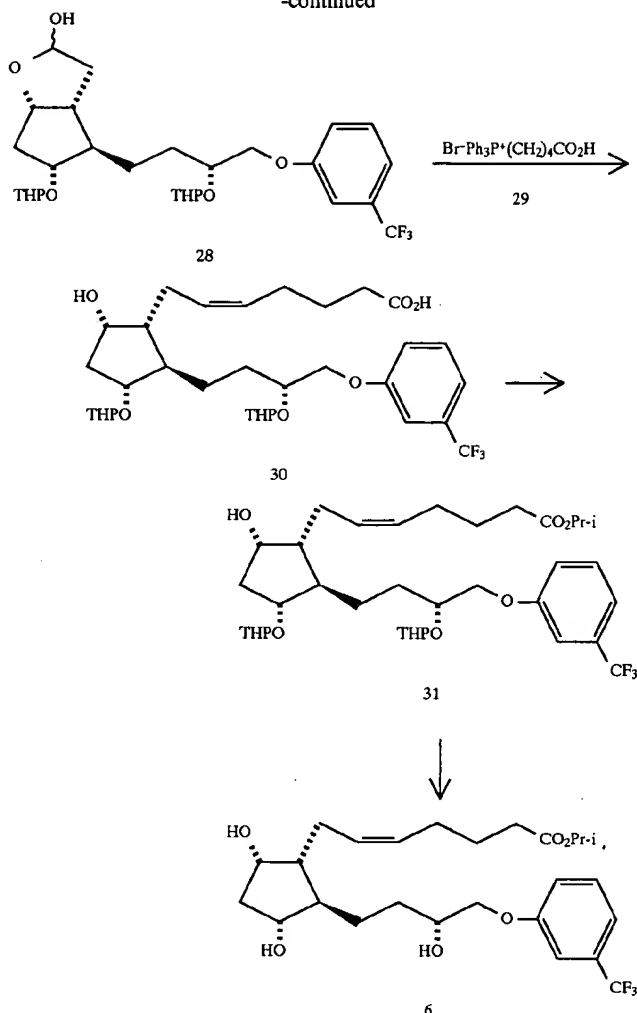
To 120 mg of 24 in 5 mL of methanol was added 0.4 mL of 2M HCl. After 1 h, the mixture was added to 3 mL of saturated $NaHCO_3$, and the resulting mixture was extracted with ethyl acetate (3×8 mL). Combined organic layers were dried over $MgSO_4$, filtered, concentrated. The resulting residue was then chromatographed on silica gel eluting with ethyl acetate to afford 54 mg (56%) of 5. ^{13}C NMR ($CDCl_3$) δ 169.92 (C), 159.26 (C), 135,13 (CH), 134.95 (CH), 134.81 (C), 124.93 (CH), 121.22 (CH), 115.06 (CH), 113.08 (CH), 77.75 (CH), 72.02 (CH), 71.94 (CH_2), 70.76 (CH_2), 68.77 (CH), 67.78 (CH_2), 66.50 (CH_2), 55.46 (CH), 49.93 (CH), 42.47 (CH_2), 25.85 (CH_2), 21.75 (CH_3). Cl MS, m/z calcd. for $C_{24}H_{34}O_7Cl_1(MH^+)$, 469.1993, found 469.1993.

EXAMPLE 2: Synthesis of 13,14-Dihydrofluprostenol Isopropyl Ester

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A: (3aR, 4R, 5R, 6aS)-5-Hydroxy-4-[(3R)-4-(3-trifluoromethylphenoxy)-3-hydroxy-1-butyl]-hexahydro-2H-cyclopenta[b]furan-2-one (26)

A mixture of 1.2 g (3.2 mmol) of diol 25 (for synthesis of diol 25, see U.S. Pat. No. 4,321,275) and 0.05 g of 10% (wt/wt) Pd/C in 20 mL of methanol was hydrogenated at 30 psi for 1.5 hours. After filtration through a short pad of Celite® concentration afforded 1.2 g (100%)of 26 as a colorless oil. ¹H NMR (CDCl₃) δ 7.44 (m, 2 H), 7.12 (m, 2 H), 4.95 (dt, 1 H), 4.15–3.80 (m, 4 H), 2.82 (dd, J=10.8, 1 H), 2.55 (m, 2 H), 2.3 (m, 1 H), 2.1–1.3 (m, 6 H).

B: (3aR, 4R, 5R, 6aS)-5-(Tetrahydropyran-2-yloxy)-4-[(3R)-4-(3-trifluoromethylphenoxy)-3-(tetrahydropyran-2-yloxy)-1-butyl]-hexahydro-2H-cyclopenta[b]furan-2-one (27)

A mixture of 1.2 g (3.2 mmol) of diol 26 and 0.05 g of ptoluenesulfonic acid monohydrate in 100 mL of CH₂Cl₂ at 0° C. was treated with 3,4-dihydro-2H-pyran (1.1 ml, 12 mmol) and the solution was stirred for 2 h at 0° C. After pouring into saturated NaHCO₃, phases were separated and the organic layer was dried over MgSO₄, filtered, concentrated, and purified by chromatography on silica gel (1/1, hexanes/EtOAc) to afford 1.1 g of 27 as a clear,

colorless oil. ¹H NMR (CDCl₃) δ 8.04 (dd, J=7.0, 1.6, 1 H), 7.44 (m, 2 H), 7.12 (m, 1 H), 4.95 (dt, 1 H), 4.8 (m, 1 H), 4.7 (m, 2 H), 4.15–3.80 (m, 4 H), 3.5 (m, 2 H), 2.82 (dd, J=10.8,1 H), 2.55 (m, 2 H), 2.3 (m, 1 H), 2.1–1.3 (m, 6 H).

C: (5Z)-(9S, 11R, 15R)-11,15-Bis(tetrahydropyran-2-yloxy)-9-hydroxy-17,18,19,20-tetranor-16-(3-trifluoromethylphenoxy)-5-prostenoic Acid Isopropyl Ester (31)

To a solution of 2.1 g (3.9 mmol) of 27 in 100 mL of THF at −78° C. was added 3.9 mL (5.8 mmol) of a 1.5M solution of diisobutyaluminum hydride in toluene. The solution was stirred for 2 h, then quenched by the sequential addition of 0.4 mL of isopropanol at −78° C. followed by 0.4 mL of water at 23° C. Volatiles were removed under reduced pressure and the aqueous solution was extracted with Et₂O/EtOAc (1/1). Organic extracts were dried over MgSO₄, filtered, and concentrated to furnish 1.9 g of lactol 28.

To a 250 mL 3-necked round bottom flask equipped with a mechanical stirrer and a thermometer were added anhydrous DMSO (100 mL) and NaH (80% dispersion in mineral oil; 0.48 g, 16 mmol). The mixture was heated to 75° C. (internal) for 30 min, after which it was allowed to cool to room temperature for 1 h. Phosphonium bromide 29 (3.5 g,

8 mmol) was then added. After stirring for 30 minutes, 1.9 g (3.5 mmol) of lactol 28 in 50 mL of DMSO was added, and the resulting solution was heated to 50° C. for 2 h and then brought to room temperature for 16 h. The solution was poured into 100 mL of water and approximately 2 mL of 50% NaOH added. The aqueous phase was extracted with ether (3×100 mL), then made acidic (pH=5.5) by the addition of a 10% citric acid solution, and extracted with EtO/hexanes, 2/1 (3×100 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated to afford 1.9 g of 30 as a colorless oil.
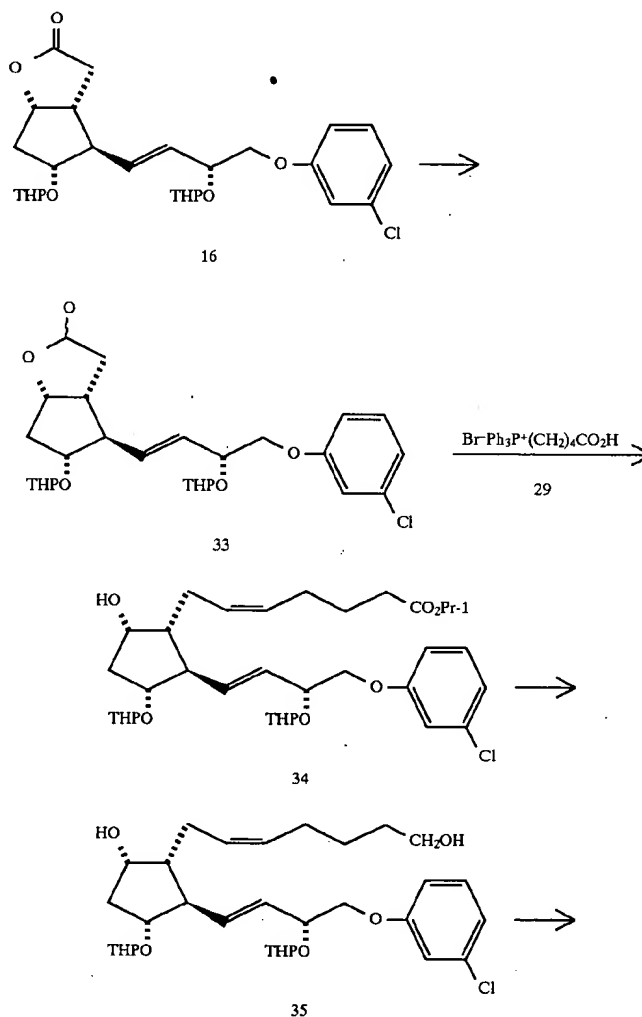
To 1.9 g of carboxylic acid 30 dissolved in 10 mL acetone was added 0.95 g (6.0 mmol) of DBU and 1.0 g (6.1 mmol) of isopropyl iodide at 23° C. After 16 h, the solution was poured into 100 mL of water and extracted with 100 mL of EtOAc. The organic extract was dried over MgSO₄, filtered, concentrated, and purified by silica gel chromatography (3/2, hexanes/EtOAc) to afford 1.9 g of isopropyl ester 31 as a colorless oil. ^{1}H NMR (CDCl₃) δ 7.44 (t, 1 H), 7.12 (d, 1 H), 7.12 (dd, 2 H), 5.5–5.3 (m, 2 H), 4.99 (heptet, 1 H), 4.15–3.80 (m, 4 H), 2.82 (dd, J=10.8, 1 H), 2.55 (m, 2 H), 2.3 (m, 1 H), 2.1–1.3 (m, 24 H), 1.23 (s, 3 H), 1.20 (s, 3 H).
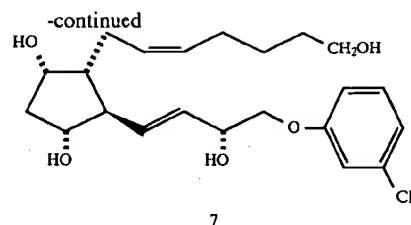
D: (5Z)-(9S, 11R, 15R)-17,18,19,20-Tetranor-16-(3-trifluoromethylphenoxy)-9,11,15-trihydroxy-5-prostenoic Acid Isopropyl Ester (6)

Ester 31 (1.9 g, 2.8 mmol) was dissolved in 14 mL of a mixture of AcOH/THF/H₂O (4/2/1) and the solution was heated to 50° C. for 1 h, allowed to cool to 23° C., poured into a saturated solution of NaHCO₃, and extracted with Et₂O (2×100 mL) and EtOAc (100 mL). The combined organic extracts were dried over MgSO₄, filtered, concentrated, and purified by silica gel chromatography (1/1, hexanes/EtOAc) to furnish 0.5 g of triol 6 as a clear, colorless oil. ^{1}H NMR (CDCl₃) δ 7.44 (t, J=7.8,1 H), 7.12 (dd, J=7.8, 2.0, 1 H), 7.12 (ddd, J=15.6, 7.2, 2.0, 2 H), 5.5–5.3 (m, 2 H), 4.99 (heptet, J=6.3, 1 H), 4.15–3.80 (m, 4 H), 3.2 (d, 1 H), 2.95 (s, 1 H), 2.82 (dd, J=10.8, 1 H), 2.75 (d, J=5.9, 1 H), 2.55 (m, 2 H), 2.3 (m, 1 H), 2.1–1.3 (m, 24 H), 1.23 (s, 3 H), 1.20 (s, 3 H). ^{13}C NMR (CDCl₃) δ 173.5, 158.7, 132.1, 131.5,130.0, 129.5, 129.2, 123.3, 120.8, 117.7, 117.6, 111.4, 111.4, 78.6, 74.4, 72.4, 69.9, 67.6, 52.6, 51.7, 42.5, 34.0, 31.5, 29.4, 26.8, 26.6, 24.9, 21.7.

EXAMPLE 3: Synthesis of Cloprostenol-1-ol (7)

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Br⁻Ph₃P⁺(CH₂)₄CO₂H
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A: (5Z, 13E)-(9S, 11R, 15R)-11,15-Bis(tetrahydropyran-2-yloxy)-16-(3chlorophenoxy)-9-hydroxy-17,18,19,20-tetranor-5,13-prostadienoic Acid Isopropyl Ester (34)

A 1.5M solution of diisobutylaluminum hydride in toluene (10 mL, 15 mmol) was added dropwise to a solution of 5.8 g (11.4 mmol) of lactone 16 in 55 mL of THF at −78° C. After 1 h, 10 mL of methanol was added dropwise, and the mixture was stirred for 10 min at −78° C. before being warmed to room temperature. The mixture was then poured into 100 mL of a 1/1 solution of saturated aqueous potassium sodium tartrate/ethyl acetate and stirred. After separating layers, the aqueous phase was extracted with ethyl acetate (2×40 mL). Combined organic layers were dried over MgSO$_4$, filtered, concentrated, and purified by silica gel chromatography (3/2, ethyl acetate/hexane), to afford 4.4 g (76%) of lactol 33, which was used immediately in the next step.

A 1M solution of potassium t-butoxide in THF (50.0 ml) was added dropwise to 12.1 g (27.3 mmol) of phosphonium salt 29 in 100 mL of THF at 0° C. After 30 min, a solution of 4.4 g (8.6 mmol) of lactol 33 in 20 mL of THF was added dropwise, and the mixture was stirred at room temperature overnight. The solution was then poured into 150 mL of a 1/1 mixture of ethyl acetate/saturated NH$_4$Cl. Layers were separated and the aqueous layer was extracted with ethyl acetate (2×100 mL). Combined organic layers were dried over MgSO$_4$, filtered, concentrated, and the residue was redissolved in 80 mL of acetone. To this was added 6.5 g (45 mmol) of DBU followed by 7.3 g (43 mmol) of isopropyl iodide. After stirring overnight, the reaction was poured into 100 mL of a 1/1 mixture of ethyl acetate/saturated NH$_4$Cl. Layers were then separated and the aqueous phase was
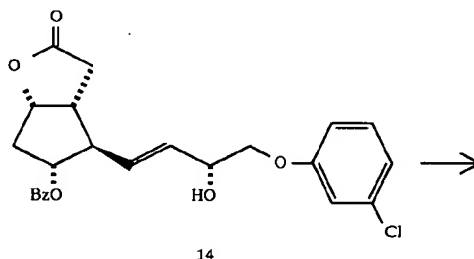
further extracted with ethyl acetate (2×100 mL). The combined organic layers were dried over MgSO$_4$, filtered, concentrated, and purified by silica gel chromatography (40% ethyl acetate in hexane) to afford 2.92 g (53% from lactone 16) of ester 34.

B: (5Z, 13E)-(9S, 11R, 15R)-16-(3-Chlorophenoxy)-17,18,19,20-tetranor-9,11,15-trihydroxy-5,13-prostadienol (7)

A solution of 500 mg (0.79 mmol) of 34 in 10 mL of THF was added dropwise to 61 mg (1.60 mmol) of lithium aluminum hydride in 20 mL of THF at 0° C. After 40 min, the reaction was carefully poured into 15 mL of saturated NH$_4$Cl, and the mixture was then extracted with ethyl acetate (3×40 mL). Combined organic layers were dried over MgSO4 , filtered, and concentrated to afford 500 mg of crude 35.

To a solution of 500 mg of 35 in 20 mL of methanol was added 0.5 mL of 2M HCl. After 1 h, the reaction was quenched with 20 mL of saturated NaHCO$_3$ and the mixture was extracted with ethyl acetate (4×30 mL). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated. Silica gel s chromatography (EtOAc) provided 101 mg (31% from 34) of 7. ^{13}C NMR (CDCl$_3$) δ 159.27 (C), 135.44 (CH), 134.82 (C), 130.64 (CH), 130.26 (CH), 128.23 (CH), 121.25 (CH), 115.07 (CH), 113.08 (CH), 77.35 (CH), 72.35 (CH), 71.90 (CH$_2$), 70.89 (CH), 62.22 (CH$_2$), 55.40 (CH), 49.87 (CH), 42.79 (CH$_2$), 31.83 (CH$_2$), 26.77 (CH$_2$), 25.60 (CH$_2$), 25.33 (CH$_2$). Cl MS m/z calcd for C$_{22}$H$_{32}$O$_5$Cl$_1$ (MH$^+$) 411.1938, found 411.1938.

EXAMPLE 4: Synthesis of 13,14-
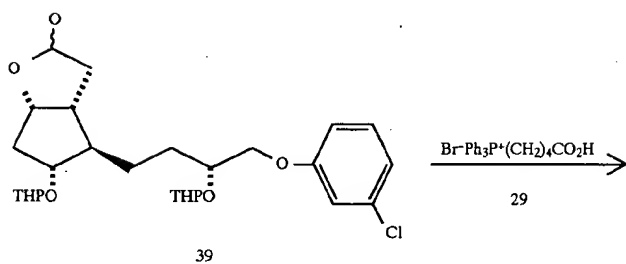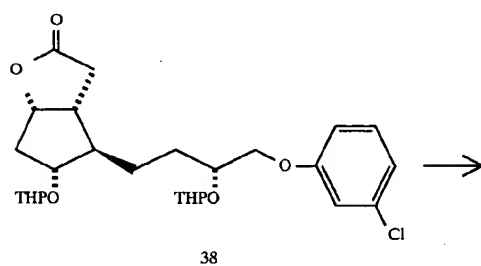Dihydrocloprostenol-1-ol Pivaloate (8)

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$$\xrightarrow{\text{Br}^-\text{Ph}_3\text{P}^+(\text{CH}_2)_4\text{CO}_2\text{H}}$$
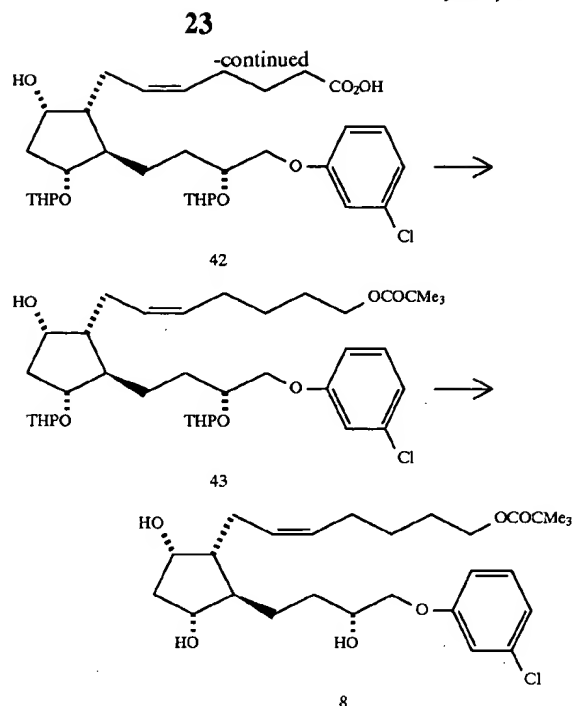
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A: (3aR, 4R, 5R, 6aS)-4-[(3R)-4-(3-Chlorophenoxy)-3-hydroxybutyl]-5-hydroxy-hexahydro-2H-cyclopenta[b]furan-2-one (37):

A mixture of 2.4 g (5.4 mmol) of 14 and 250 mg of 10% (wt/wt) Pd/C in 35 mL of ethyl acetate was hydrogenated at 40 psi for 1 h. After filtration through a short pad of Celite®, the filtrate was evaporated down to 2.3 g (100%) of hydrogenated product 36.

The crude benzoate 36 was dissolved in 25 mL of methanol, and 610 mg (4.4 mmol) of K₂CO₃ was added. After 3.5 h, the mixture was poured into 100 mL of water/ethyl acetate (1/1). Layers were separated, and the aqueous phase was further extracted with ethyl acetate (2×50 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated. Silica gel chromatography (EtoAc) provided 1.50 g (82%) of 37 as a white solid, m.p.=102.0°–103.5° C. ¹H NMR δ 7.22 (t, J=8.2 Hz, 1 H), 7.0–6.94 (m, 1 H), 6.91–6.88 (t, J=2.1 Hz, 1 H), 6.83–6.77 (m, 1 H), 4.97 (dt, J=3.0, 8.3 Hz, 1 H), 4.12–3.91 (m, 3 H), 3.82 (dd, J=7.4, 9.0 Hz, 1 H), 2.85 (dd, J=8.0, 16.5 Hz, 1 H), 2.6–1.4 (m, 11 H).

B: (3aR, 4R, 5R, 6aS)-4-[(3R)-4-(3-Chlorophenoxy)-3-(tetrahydropyran-2-yloxy)bulyl]-5-(tetrahydropyran-2-yloxy)-hexahydro-2H-cyclogenta[b]furan-2-one (38)

Diol 37 (3.4 g, 10 mmol) and 2.2 g (26 mmol) of 3,4-dihydro-2H-pyran were dissolved in 80 mL of CH₂Cl₂, and 240 mg (1.3 mmol) of p-toluenesulfonic acid monohydrate was added at 0° C. After 1 h, the reaction was poured into 50 mL of saturated NaHCO₃ and the mixture was extracted with CH₂Cl₂ (3×40 mL). The combined organic layers were dried over MgSO₄, filtered, concentrated, and the residue was chromatographed on silica gel (hexane/ethyl acetate, 1/1) to afford 4.5 g (87%) of bis-THP ether 38.

C: (5Z)-(9S, 11R, 15R)-11,15-Bis(tetrahydropyran-2-yloxy)-16-(3-chlorophenoxy)-9-hydroxy-17,18,19,20-tetranor-5-prostenoic Acid IsoproDVl Ester (41)

A 1.5M solution of diisobutylaluminum hydride in toluene (1.8 mL, 2.7 mmol) was added to the solution 1.05 g

(2.06 mmol) of 38 in 10 mL of THF at –78° C. After 1 h, 4 mL of methanol was added and the mixture was warmed to 25° C., then poured into 40 mL of ethyl acetate/saturated aqueous potassium sodium tartrate (1/1). Layers were separated and the aqueous phase was further extracted with ethyl acetate (3×30 mL). The combined organic layers were then dried over MgSO₄, filtered, concentrated, and the residue was chromatographed on silica gel (ethyl acetate) to afford 740 mg (70%) of lactol 39.

A 1.5M solution of potassium t-butoxide in THF (8.6 mL, 8.6 mmol) was added dropwise to a mixture of 15 mL of THF and 1.92 g (4.33 mmol) of phosphonium salt 29 at 0° C. After stirring for 1 h, a solution of 740 mg (1.45 mmol) of lactol 39 in 5 mL of THF was added dropwise, and the reaction was allowed to warm to 25° C. overnight. The mixture was then poured into 100 mL of ethyl acetate/saturated NH₄Cl (1/1). Layers were separated, and the aqueous phase was further extracted with ethyl acetate (2×70 mL). Combined organic layers were dried over MgSO₄, filtered, and concentrated to afford 1.6 g of crude acid 40.

Crude acid 40 (1.6 g) was dissolved in 11 mL of acetone and cooled to 0° C., then 850 mg (5.6 mmol) of DBU was added dropwise to the solution. The resulting mixture was stirred for 15 min at 0° C. and 30 min at 25° C., after which 850 mg (5.0 mmol) of isopropyl iodide was added. The reaction was stirred overnight and poured into 100 mL of ethyl acetate/saturated NH₄Cl (1/1). Layers were separated, and the aqueous phase was further extracted with ethyl acetate (2×50 mL). Combined organic layers were dried over MgSO₄, filtered and concentrated. The resulting residue was purified by silica gel chromatography (ethyl acetate/hexanes, 3/2) to afford 560 mg (61 % from lactol 39) of isopropyl ester 41.

D: (5Z)-(9S, 11R, 15R)-16-(3-Chlorophenoxy)-17,18,19,20-tetranor-9,11,15-trihydroxy-5-prostenol Pivaloate (8)

A solution of 400 mg (0.63 mmol) of 41 in 5 mL of THF was added dropwise to a suspension of 35 mg (0.92 mmol)

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of lithium aluminum hydride in 5 mL of THF at 0° C. After 2 h, the reaction was poured into 50 mL of a 1/1 mixture of ethyl acetate/saturated $NaHCO_3$. The layers were then separated, and the aqueous phase was extracted with ethyl acetate (2×2 mL). Combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by silica gel chromatography (ethyl acetate) to afford 350 mg (95%) of diol 42.

Pivaloyl chloride (90 mg, 0.75 mmol) was added to a mixture of 350 mg (0.60 mmol) of 42, 60 mg (0.76 mmol) of pyridine, 22 mg (0.18 mmol) of 4(dimethylamino) pyridine, and 7 mL of CH_2Cl_2. After 1.5 h, the mixture was poured into 30 mL of saturated NH_4Cl/ethyl acetate (1/1). Layers were then separated and the aqueous phase was extracted with ethyl acetate (2×20 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and purified by silica gel chromatography (ethyl acetate/hexane, 3/2) to afford 370 mg (93%) of pivaloate 43.

Water (approximately 10 drops) and concentrated HCl (approximately 3 drops) were added to a solution of 370 mg (0.56 mmol) of 43 in 5 mL of methanol. After stirring overnight, the reaction was quenched by the addition of 20 mL of saturated $NaHCO_3$, and the mixture was extracted with ethyl acetate (3×20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed on silica gel (ethyl acetate/ hexane, 3/2), to afford 165 mg (59%) of triol 8. ^{13}C NMR ($CDCl_3$) δ 178.77 (C), 159.27 (C), 134.80 (C), 130.20 (CH), 128.62 (CH), 121.19 (CH), 114.97 (CH), 112.97 (CH), 78.50 (CH), 74.46 (CH), 72.31 (CH_2), 69.86 (CH), 64.16 (CH_2), 52.53 (CH), 51.67 (CH), 42.50 (CH_2), 31.51 (CH_2), 29.40 (OH_2), 28.10 (OH_2), 27.12 (OH_3), 26.77 (CH_2), 26.65 (CH_2), 25.77 (CH_2). Cl MS, m/z calcd for $C_{27}H_{41}O_6Cl_1$ (MH⁺), 497.2670, found 497.2656

EXAMPLE 5

$PGF_{2\alpha}$ analogues are known to contract the iris sphincter of cats and this assay is a generally accepted reference for activity. For this reason, the pupil diameter of cats may be used to define the activity of $PGF_{2\alpha}$ analogues and, as demonstrated by Stjernschantz and Resul (*Drugs Future*, 17:691–704 (1992)), predict the IOP-lowering potency.

Compounds of the present invention were therefore screened for pupillary constriction in the cat. Data for compounds 6, 7, and 8 are presented in Table 2, below. The response is quantitated as $Area_{1-5}$ values (area under the pupil diameter versus time curve from 1–5 hours), and the equivalent response dose (ED_5) is estimated from its dose response relationship.

TABLE 2

Cat Pupil Diameter Response	
Compound	ED_5 (μg)
$PGF_{2\alpha}$ Isopropyl Ester	0.02
Cloprostenol Isopropyl Ester	0.01
6	0.2
7	0.02
8	0.06

Discussion:

The two standard compounds, $PGF_{2\alpha}$isopropyl ester and cloprostenol isopropyl ester, produced marked change in cat pupillary diameter, displaying ED_5 values of 0.02 and 0.01 jig, respectively. Compound 7 (cloprostenol-1-ol) and com-

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pound 8 (13,14-dihydrocloprostenol-1-ol pivaloate), displayed nearly equivalent potency. 13,14-Dihydrofluprostenol isopropyl ester (compound 6) was approximately one order of magnitude less potent, with an ED_5 of 0.2 μg.

EXAMPLE 6

In the study presented below, compound 6 (Table 1, above) was tested for IOP-lowering effect in cynomolgus monkey eyes.

The right eyes of the cynomolgus monkeys used in this study were previously given laser trabeculoplasty to induce ocular hypertension in the lasered eye. Animals had been trained to sit in restraint chairs and conditioned to accept experimental procedures without chemical restraint. IOP was determined with a pneumatonometer after light corneal anesthesia with dilute proparacaine. The test protocol included a five-dose treatment regimen because of the typical delayed response to prostaglandins. The designated test formulations were administered to the lasered right eyes, and the normal left eyes remained untreated, although IOP measurements were taken. Baseline IOP values were determined prior to treatment with the test formulation, and then IOP was determined from 1 to 7 hours after the first dose, 16 hours after the fourth dose, and 1 to 4 hours after the fifth dose.

The equivalent response dose (ED_{20}) is estimated from the dose response relationship to be the dose producing a 20% peak reduction in IOP.

TABLE 3

Monkey IOP Response	
Compound	ED_{20} (μg)
$PGF_{2\alpha}$ Isopropyl Ester	0.4
6	0.3

Discussion:

As can be seen in Table 3, compound 6, the 13,14-dihydro analogue of fluprostenol was quite potent in the monkey IOP model, producing a 20% reduction at 0.3 μg. This was even more potent than the standard compound, $PGF_{2\alpha}$isopropyl ester.

EXAMPLE 7

The following Formulations 1–4 are representative pharmaceutical compositions of the invention for topical use in lowering of intraocular pressure. Each of Formulations 1 through 4 may be formulated in accordance with procedures known to those skilled in the art.

FORMULATION 1

Ingredient	Amount (wt %)
Compound 5 (Table 1)	0.002
Dextran 70	0.1
Hydroxypropyl methylcellulose	0.3
Sodium chloride	0.77
Potassium chloride	0.12
Disodium EDTA	0.05
Benzalkonium chloride	0.01
HCl and/or NaOH	pH 7.2–7.5
Purified water	q.s. to 100%

FORMULATION 2

Ingredient	Amount (wt %)
Compound 6 (Table 1)	0.01
Monobasic sodium phosphate	0.05
Dibasic sodium phosphate (anhydrous)	0.15
Sodium chloride	0.75
Disodium EDTA	0.01
Benzalkonium chloride	0.02
Polysorbate 80	0.15
HCl and/or NaOH	pH 7.3–7.4
Purified water	q.s.to 100%

FORMULATION 3

Ingredient	Amount (wt %)
Compound 7 (Table 1)	0.001
Dextran 70	0.1
Hydroxypropyl methylcellulose	0.5
Monobasic sodium phosphate	0.05
Dibasic sodium phosphate (anhydrous)	0.15
Sodium chloride	0.75
Disodium EDTA	0.05
Benzalkonium chloride	0.01
NaOH and/or HCl	pH 7.3–7.4
Purified water	q.s. to 100%

FORMULATION 4

Ingredient	Amount (wt %)
Compound 8 (Table 1)	0.003
Monobasic sodium phosphate	0.05
Dibasic sodium phosphate (anhydrous)	0.15
Sodium chloride	0.75
Disodium EDTA	0.05
Benzalkonium chloride	0.01
HCl and/or NaOH	pH 7.3–7.4
Purified water	q.s. to 100%

The invention has been described by reference to certain preferred embodiments; however, it should be understood that it may be embodied in other specific forms or variations thereof without departing from its spirit or essential characteristics. The embodiments described above are therefore considered to be illustrative in all respects and not restrictive, the scope of the invention being indicated by the appended claims rather than by the foregoing description.

What is claimed is:

1. A method of treating glaucoma and ocular hypertension which comprises topically administering to the affected eye a composition comprising a therapeutically effective amount of a compound having the absolute stereochemical structure of the following formula (IV), and being substantially free of the enantiomer of said compound:

wherein:

R_1 =H; C_1–C_{12} straight-chain or branched alkyl; C_1–C_{12} straight-chain or branched acyl; C_3–C_3 cycloalkyl; or a cationic salt moiety;

R_2, R_3 =H, or C_1–C_5 straight-chain or branched alkyl; or R_2 and R_3 taken together may represent O;

X=O, S, or CH_2;

--- represents any combination of a single bond, or a cis or trans double bond for the alpha (upper) chain; and a single bond or trans double bond for the omega (lower) chain;

R_9=H, C_1–C_{10} straight-chain or branched alkyl, or C_1–C_{10} straight-chain or branched acyl;

R_{11}=H, C_1–C_{10} straight-chain or branched alkyl, or C_1–C_{10} straight-chain or branched acyl;

Y=O; or H and OR_{15} in either configuration wherein R_{15}=H, C_1–C_{10} straightchain or branched alkyl, or C_1–C_{10} straight-chain or branched acyl; and

Z=Cl or CF_3;

with the proviso that when R_2 and R_3 taken together represent O, then $R_1 \neq C_1$–C_{12} straight-chain or branched acyl; and when R_2=R_3=H, then $R_1 \neq$ a cationic salt moiety; and

with the further proviso that the following compound be excluded:

cyclopentane heptenol-5-cis-2-(3-αhydroxy-4-m-chlorophenoxy-1-transbutenyl)-3,5 dihydroxy, [1_α, 2_β, 3_α, 5_α].

2. The method of claim 1, wherein for the compound (IV):

R_2, R_3 taken together represent O;

X=CH_2;

--- represents a cis double bond for the alpha (upper) chain and a trans double bond for the omega (lower) chain;

R_9 and R_{11}=H; and

Y=OH in the alpha configuration and H in the beta configuration.

3. The method of claim 2, wherein for the compound (IV): Z=CF_3.

4. The method of claim 1, wherein: R_2 =R_3=H, or R_2 and R_3 taken together represent O; X=O or CH_2; R_9=R_{11}=H; Y=H and OR_{15}; and R_{15}=H.

5. The method of claim 4, wherein: R_1=H, C_1–C_{12} straight chain or branched alkyl or cationic salt moiety; and R_2 and R_3 taken together represent O.

6. The method of claim 5, wherein the compound of formula (IV) is selected from the group consisting of 3-oxacloprostenol, 13,14-dihydrofluprostenol, and their pharmaceutically acceptable esters and salts.

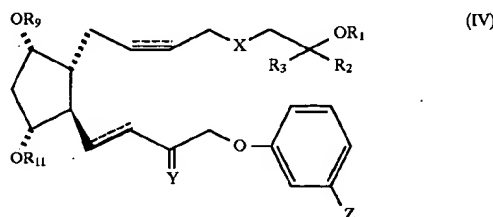7. The method of claim 4, wherein: R_1 =H or C_1–C_{12} straight chain or branched acyl; and R_2=R_3=H.

8. The method of claim 7, wherein the compound formula (IV) is 13,14dihydrocloprostenol pivaloate.

9. The method of claim **1**, wherein between about 0.01 and about 1000 μg/eye of the compound is administered.

10. The method of claim **9**, wherein between about 0.1 and about 100 μg/eye of the compound is administered.

11. The method of claim **10**, wherein between about 0.1 and about 10 μg/eye of the compound is administered.

12. A topical ophthalmic composition for the treatment of glaucoma and ocular hypertension comprising an ophthalmically acceptable carrier and a therapeutically effective amount of a compound having the absolute stereochemical structure of the following formula (IV), and being substantially free of the enantiomer of said compound:

(IV)

wherein:

R_1=H; C_1–C_{12} straight-chain or branched alkyl; C_1–C_{12} straight-chain or branched acyl; C_3–C_8 cycloalkyl; or a cationic salt moiety;

R_2, R_3=H, or C_1–C_5 straight-chain or branched alkyl; or R_2 and R_3 taken together may represent O;

X=O, S, or CH_2;

---represents any combination of a single bond, or a cis or trans double bond for the alpha (upper) chain; and a single bond or trans double bond for the omega (lower) chain;

R_9=H, C_1–C_{10} straight-chain or branched alkyl, or C_1–C_{10} straight-chain or branched acyl;

R_{11}=H, C_1–C_{10} straight-chain or branched alkyl, or C_1–C_{10} straight-chain or branched acyl;

Y=O; or H and OR_{15} in either configuration wherein R_{15}=H, C_1–C_{10} straight-chain or branched alkyl, or C_1–C_{10} straight-chain or branched acyl; and

Z=Cl or CF_3;

with the proviso that when R_2 and R_3 taken together represent O, then $R_1 \neq C_1$–C_{12} straight-chain or branched acyl; and when R_2 =R_3 =H, then $R_1 \neq$ a cationic salt moiety; and

with the further proviso that the following compound be excluded:

cyclopentane heptenol-5-cis-2-(3-μhydroxy4-m-chlorophenoxy-11-transbutenyl)-3,5 dihydroxy, [1_α, 2_β, 3_α, 5_α].

13. The composition of claim **12**, wherein for the compound (IV):

R_2, R_3 taken together represent O;

X=CH_2;

---represents a cis double bond for the alpha (upper) chain and a trans double bond for the omega (lower) chain;

R_0 and R_{11}=H; and

Y=OH in the alpha configuration and H in the beta configuration.

14. The composition of claim **13**, wherein for the compound (IV): Z=CF_3.

15. The composition of claim **12**, wherein: R_2=R_3=H, or R_2 and R_3 taken together represent O; X=O or CH_2; R_9=R_{11}=H; Y=H and OR_{15}; and R_{15}=H.

16. The composition of claim **15**, wherein: R_1=H, C_1–C_{12} straight chain or branched alkyl, or cationic salt moiety; and R_2 and R_3 taken together represent O.

17. The composition of claim **16**, wherein the compound of formula (IV) is selected from the group consisting of 3-oxacloprostenol, 13,14-dihydrofluprostenol, and their pharmaceutically acceptable esters and salts.

18. The composition of claim **15**, wherein: R_1=H or C_1–C_{12} straight chain or branched acyl; and R_2=R_3=H.

19. The composition of claim **18**, wherein the compound of formula (IV) is dihydrocloprostenol pivaloate.

20. The composition of claim **12**, wherein the concentration of the compound of formula (IV) is between about 0.0003 and about 0.3 wt %.

21. The composition of claim **20**, wherein the concentration of the compound of formula (IV) is between about 0.0003 and about 0.3 wt %.

22. The composition of claim **21**, wherein the concentration of the compound of formula (IV) is between about 0.003 and about 0.03 wt %.

* * * * *

United States Patent [19]

Burk

[11] **Patent Number:** 5,834,498

[45] **Date of Patent:** Nov. 10, 1998

[54] **CYCLOPENTANE HEPTAN(ENE)OIC ACID, 2-HETEROARYLALKENYL DERIVATIVES AS THERAPEUTIC AGENTS**

[75] Inventor: **Robert M. Burk**, Laguna Beach, Calif.

[73] Assignee: **Allergan**, Waco, Tex.

[21] Appl. No.: **726,921**

[22] Filed: **Oct. 7, 1996**

Related U.S. Application Data

[63] Continuation of Ser. No. 443,992, May 18, 1995, abandoned, which is a continuation-in-part of Ser. No. 605,567, Feb. 22, 1996, Pat. No. 5,688,819, which is a continuation-in-part of Ser. No. 371,339, Jan. 11, 1995, Pat. No. 5,607,978, which is a continuation of Ser. No. 154,244, Nov. 18, 1993, abandoned, which is a division of Ser. No. 948,056, Sep. 21, 1992, Pat. No. 5,352,708.

[51] **Int. Cl.^{6}** A61K 31/38; A61K 31/34; C07D 333/38; C07D 307/38

[52] **U.S. Cl.** 514/445; 514/438; 514/461; 514/447; 514/448; 514/471; 514/472; 514/473; 549/61; 549/62; 549/68; 549/70; 549/74; 549/449; 549/450; 549/452; 549/66; 549/69; 549/72; 549/73; 549/75; 549/76; 549/77; 549/79; 549/455; 549/63; 549/64; 549/65

[58] **Field of Search** 549/79, 78, 76, 549/75, 73, 72, 70, 68; 514/438, 447, 448

[56] References Cited

U.S. PATENT DOCUMENTS

3,845,115	10/1974	Lincoln, Jr. et al.	562/503
3,847,967	11/1974	Lincoln, Jr. et al.	560/121
3,853,950	12/1974	Lincoln et al.	560/121
4,256,745	3/1981	Skuballa et al.	424/248.55
4,304,783	12/1981	Beck et al.	514/530
4,585,791	4/1986	Faustini et al.	514/471
4,599,353	7/1986	Bito	514/530
4,994,274	2/1991	Chan et al.	424/427
5,006,539	4/1991	Jones et al.	514/357
5,028,624	7/1991	Chan et al.	514/530
5,034,413	7/1991	Chan et al.	514/530
5,238,961	8/1993	Woodward et al.	514/573
5,270,049	12/1993	Chan, II et al.	424/427
5,296,504	3/1994	Stjernschantz et al.	514/530
5,321,128	6/1994	Sternschantz et al.	514/530
5,352,708	10/1994	Woodward et al.	514/729
5,422,368	6/1995	Strenschantz et al.	514/530
5,422,369	6/1995	Sternschantz et al.	514/530

FOREIGN PATENT DOCUMENTS

0364417	4/1990	European Pat. Off. .
0 603 800	6/1994	European Pat. Off. .
90 02553	3/1990	WIPO .
94 06433	3/1994	WIPO .

OTHER PUBLICATIONS

C. Liljebris et al, *Derivatives of 17–Phenyl–18, 19, 20–trinorprostaglandin F–2–alpha Isopropyl Esters: Potential Antiglaucoma Agents*, J. Med. Chem. vol. 38, No. 2, Jan. 20, 1995, pp. 289–304.

Starr, M.S., *Exp. Eye Res.* 1971, 11 pp. 170–177.

Bito, L.Z. *Biological Protection with Prostaglandins*, Cohen, M.M., ed., Boca Raton, Fla, CRC Press Inc., 1995, pp. 231–252.

Bito, L.Z. *Applied Pharmacology in the Medical Treatment of Glaucoma*, Drance, S.M. & Neufeld, A.H. eds., New York, Brune & Stratton, 1984, pp. 477–505.

Nilsson et al, *Inv. Ophthalmol. Vis. Sci.* 28 (suppl), 1987, p. 284.

Bito, L.Z., *Arch. Ophthalmol.* 105, 1987, 1036.

Siebold et al, *Prodrug*, 5, 1987, 3.

Primary Examiner—Deborah C. Lambkin
Attorney, Agent, or Firm—Robert J. Baran; Martin A. Voet; Howard R. Lambert

[57] ABSTRACT

The invention relates to the use of derivatives of F-type prostaglandins as ocular hypotensives. The PGF derivatives used in accordance with the invention are represented by the following formula I:

wherein wavy line attachments indicate either the alpha (α) or beta (β) configuration; hatched segments indicate α configuration, solid triangles are used to indicate β configuration, dashed bonds represent a double bond, or a single bond, R is a substituted heteroaryl radical, R^1 is hydrogen or a lower alkyl radical having up to six carbon atoms, X is selected from the group consisting of —OR^1 and —$N(R^1)_2$, Y is =O or represents 2 hydrogen radicals. Certain of the compounds represented by Formula I comprise another aspect of the present invention.
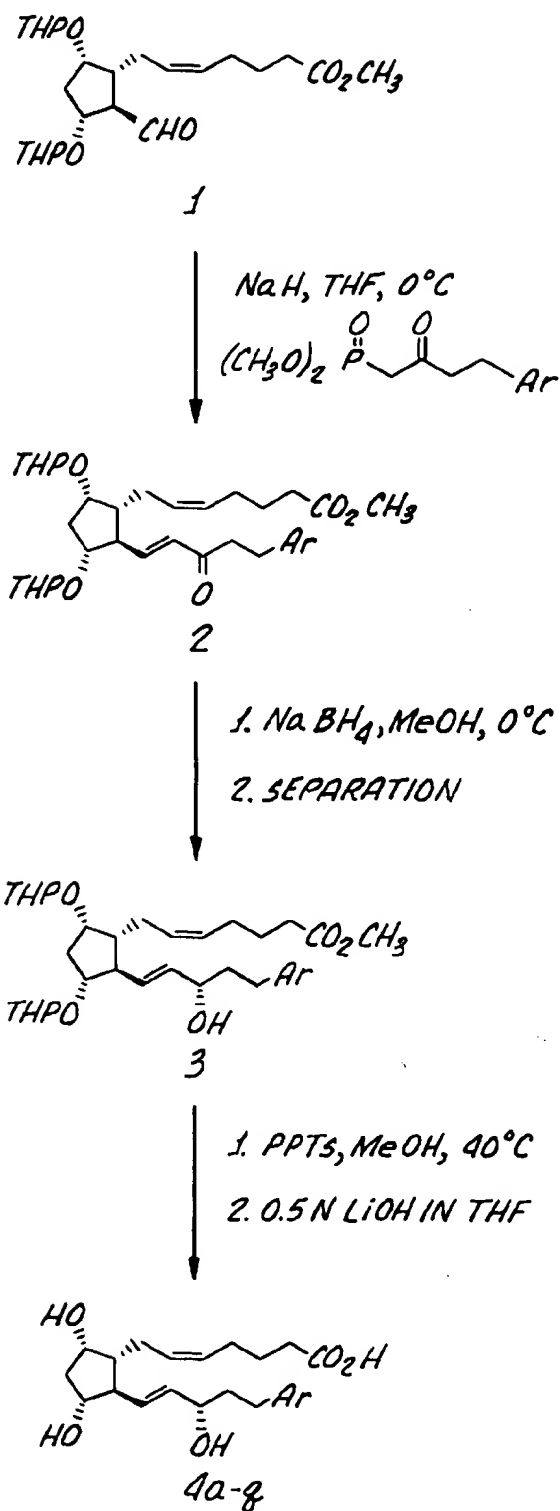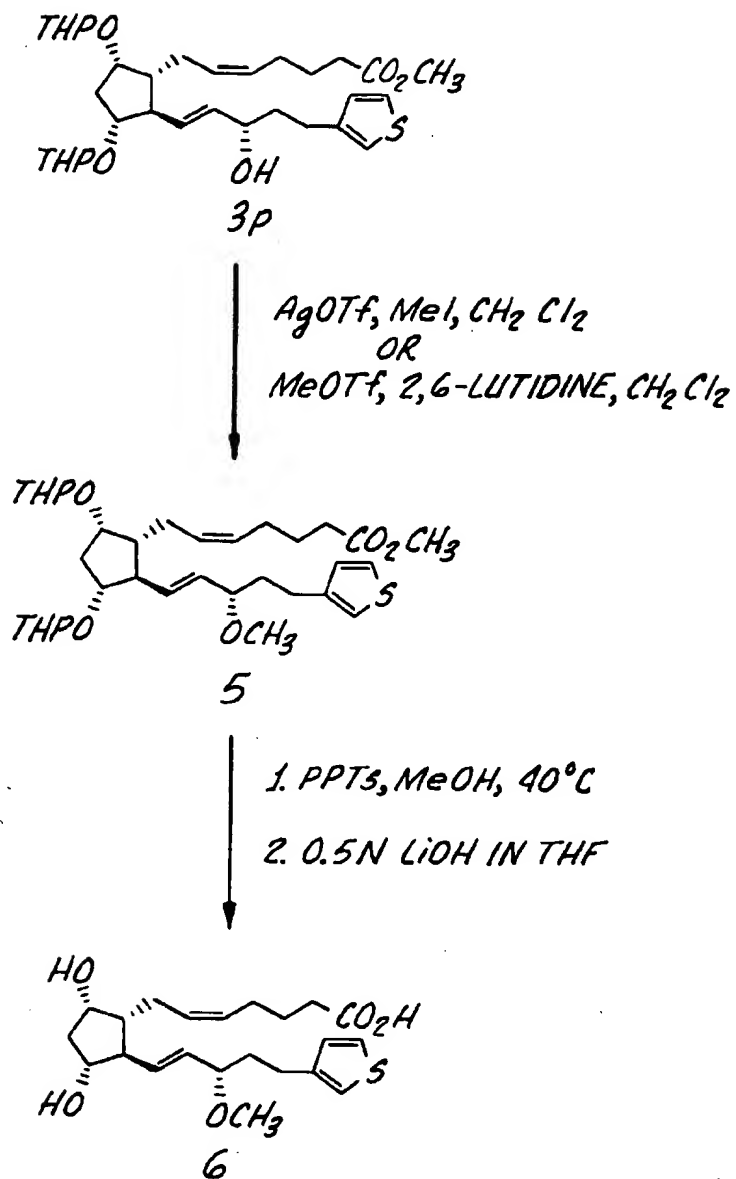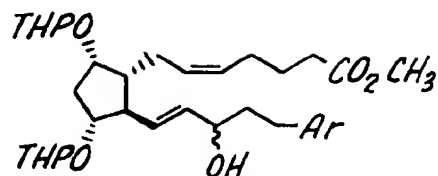
47 Claims, 5 Drawing Sheets

FIG. 1.

_FIG. 2.

FIG. 3.

THPO

THPO

CO_2CH_3

Ar

OH

3p α-OH

3q β-OH

3r α-OH

PPTS, MeOH, 40°C

HO

HO

CO_2CH_3

Ar

OH

7p α-OH

7q β-OH

7r α-OH

NH₄Cl
NH₃
55-60°C

HO

HO

$CONH_2$

Ar

OH

8p α-OH

8q β-OH

8r α-OH

FIG. 4.

FIG. 5.

2k

ALIQUAT 336
$Na_2S_2O_4$
$NaHCO_3$
BENZENE:H_2O, 80°C

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1. $NaBH_4$, MeOH
2. PPTs, MeOH, 45°C
3. 0.5 N LiOH IN THF
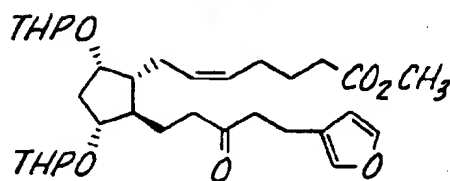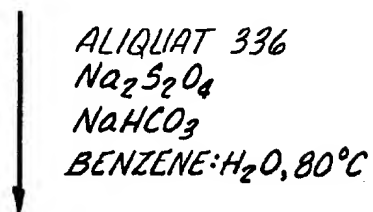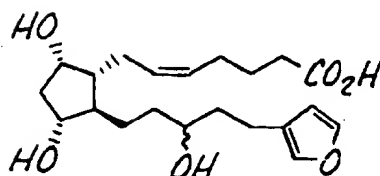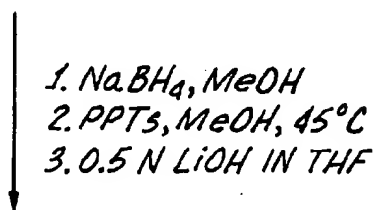
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CYCLOPENTANE HEPTAN(ENE)OIC ACID, 2-HETEROARYLALKENYL DERIVATIVES AS THERAPEUTIC AGENTS

This application is a continuation of application Ser. No. 08/443,992 filed May 18, 1995, now abandoned which is a CIP of Ser. No. 08/605,567 filed Feb. 22, 1996, now U.S. Pat. No. 5,668,819, which is a CIP of Ser. No. 08/371,339 filed Jan. 11, 1995, now U.S. Pat. No. 5,607,978; which is a continuation of Ser. No. 08/154,224 filed Nov. 18, 1993, abandoned; which is a division of Ser. No. 07/948,056 filed Sep. 21, 1992, now U.S. Pat. No. 5,352,708.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to cyclopentane heptanoic acid, 2 heteroarylalkenyl derivatives which may be substituted in the 1-position with hydroxyl, alkyloxy, amino and amido groups, e.g. 1-OH cyclopentane heptanoic acid, 2 heteroarylalkenyl derivatives. These compounds are potent ocular hypotensives and are particularly suited for the management of glaucoma.

2. Description of Related Art

Ocular hypotensive agents are useful in the treatment of a number of various ocular hypertensive conditions, such as post-surgical and post-laser trabeculectomy ocular hypertensive episodes, glaucoma, and as presurgical adjuncts.

Glaucoma is a disease of the eye characterized by increased intraocular pressure. On the basis of its etiology, glaucoma has been classified as primary or secondary. For example, primary glaucoma in adults (congenital glaucoma) may be either open-angle or acute or chronic angle-closure. Secondary glaucoma results from pre-existing ocular diseases such as uveitis, intraocular tumor or an enlarged cataract.

The underlying causes of primary glaucoma are not yet known. The increased intraocular tension is due to the obstruction of aqueous humor outflow. In chronic open-angle glaucoma, the anterior chamber and its anatomic structures appear normal, but drainage of the aqueous humor is impeded. In acute or chronic angle-closure glaucoma, the anterior chamber is shallow, the filtration angle is narrowed, and the iris may obstruct the trabecular meshwork at the entrance of the canal of Schlemm. Dilation of the pupil may push the root of the iris forward against the angle, and may produce pupilary block and thus precipitate an acute attack. Eyes with narrow anterior chamber angles are predisposed to acute angle-closure glaucoma attacks of various degrees of severity.
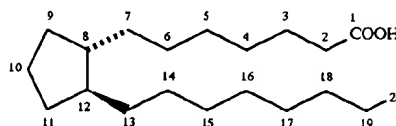
Secondary glaucoma is caused by any interference with the flow of aqueous humor from the posterior chamber into the anterior chamber and subsequently, into the canal of Schlemm. Inflammatory disease of the anterior segment may prevent aqueous escape by causing complete posterior synechia in iris bombe, and may plug the drainage channel with exudates. Other common causes are intraocular tumors, enlarged cataracts, central retinal vein occlusion, trauma to the eye, operative procedures and intraocular hemorrhage.

Considering all types together, glaucoma occurs in about 2% of all persons over the age of 40 and may be asymptotic for years before progressing to rapid loss of vision. In cases where surgery is not indicated, topical b-adrenoreceptor antagonists have traditionally been the drugs of choice for treating glaucoma.

Certain eicosanoids and their derivatives have been reported to possess ocular hypotensive activity, and have

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been recommended for use in glaucoma management. Eicosanoids and derivatives include numerous biologically important compounds such as prostaglandins and their derivatives. Prostaglandins can be described as derivatives of prostanoic acid which have the following structural formula:

Various types of prostaglandins are known, depending on the structure and substituents carried on the alicyclic ring of the prostanoic acid skeleton. Further classification is based on the number of unsaturated bonds in the side chain indicated by numerical subscripts after the generic type of prostaglandin [e.g. prostaglandin E_1 (PGE_1), prostaglandin E_2 (PGE_2)], and on the configuration of the substituents on the alicyclic ring indicated by α or β [e.g. prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$)].

Prostaglandins were earlier regarded as potent ocular hypertensives, however, evidence accumulated in the last decade shows that some prostaglandins are highly effective ocular hypotensive agents, and are ideally suited for the long-term medical management of glaucoma (see, for example, Bito, L. Z. Biological Protection with Prostaglandins, Cohen, M. M., ed., Boca Raton, Fla., CRC Press Inc., 1985, pp. 231–252; and Bito, L. Z., Applied Pharmacology in the Medical Treatment of Glaucomas Drance, S. M. and Neufeld, A. H. eds., New York, Grune & Stratton, 1984, pp. 477–505. Such prostaglandins include $PGF_{2\alpha}$, $PGF_{1\alpha}$, PGE_2, and certain lipid-soluble esters, such as C_1 to C_2 alkyl esters, e.g. 1-isopropyl ester, of such compounds.

Although the precise mechanism is not yet known experimental results indicate that the prostaglandin-induced reduction in intraocular pressure results from increased uveoscleral outflow [Nilsson et.al., Invest. Ophthalmol Vis. Sci. (suppl), 284 (1987)].

The isopropyl ester of $PGF_{2\alpha}$ has been shown to have significantly greater hypotensive potency than the parent compound, presumably as a result of its more effective penetration through the cornea. In 1987, this compound was described as "the most potent ocular hypotensive agent ever reported" [see, for example, Bito, L. Z., Arch. Ophthalmol. 105, 1036 (1987), and Siebold et.al., Prodrug 53 (1989)].
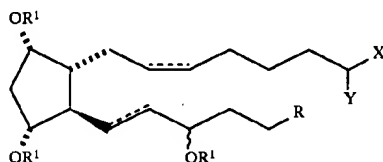
Whereas prostaglandins appear to be devoid of significant intraocular side effects, ocular surface (conjunctival) hyperemia and foreign-body sensation have been consistently associated with the topical ocular use of such compounds, in particular $PGF_{2\alpha}$ and its prodrugs, e.g., its 1-isopropyl ester, in humans. The clinical potentials of prostaglandins in the management of conditions associated with increased ocular pressure, e.g. glaucoma are greatly limited by these side effects.

In a series of co-pending United States patent applications assigned to Allergan, Inc. prostaglandin esters with increased ocular hypotensive activity accompanied with no or substantially reduced side-effects are disclosed. The co-pending U.S. Ser. No. 596,430 (filed 10 Oct. 1990), relates to certain 11-acyl-prostaglandins, such as 11-pivaloyl, 11-acetyl, 11-isobutyryl, 11-valeryl, and 11-isovaleryl $PGF_{2\alpha}$. Intraocular pressure reducing 15-acyl prostaglandins are disclosed in the co-pending application

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U.S. Ser. No. 175,476 (filed 29 Dec. 1993). Similarly, 11,15-9,15 and 9,11-diesters of prostaglandins, for example 11,15-dipivaloyl $PGF_{2\alpha}$ are known to have ocular hypotensive activity. See the co-pending patent applications U.S. Ser. Nos. 385,645 (filed 07 Jul. 1989, now U.S. Pat. No. 4,994,274), 584,370 (filed 18 Sep. 1990, now U.S. Pat. No. 5,028,624) and 585,284 (filed 18 Sep. 1990, now U.S. Pat. No. 5,034,413). The disclosures of all of these patent applications are hereby expressly incorporated by reference.

SUMMARY OF THE INVENTION

The present invention concerns a method of treating ocular hypertension which comprises administering to a mammal having ocular hypertension a therapeutically effective amount of a compound of formula I

wherein the hatched segments represent α bonds, the solid triangle represents a β bond, the wavy segment represents α or β bond, dashed lines represent a double bond or a single bond, R is a substituted heteroaryl radical, R^1 is hydrogen or a lower alkyl radical having up to six carbon atoms, X is selected from the group consisting of $-OR^1$ and $-N(R^1)_2$, Y is $=O$ or represents 2 hydrogen radicals. In a further aspect, the present invention relates to an ophthalmic solution comprising a therapeutically effective amount of a compound of formula (I), wherein the symbols have the above meanings, or a pharmaceutically acceptable salt thereof, in admixture with a non-toxic, ophthalmically acceptable liquid vehicle, packaged in a container suitable for metered application. In particular, the substituents on the heteroaryl radical may be selected from the group consisting of lower alkyl, e.g. C_1 to C_6 alkyl; halogen, e.g. fluoro, chloro and bromo; trifluoromethyl (CF_3); COR^1, e.g. $COCH_3$; $COCF_3$; SO_2NR^1, e.g. SO_2NH_2; NO_2; CN; etc.

In a still further aspect, the present invention relates to a pharmaceutical product, comprising

a container adapted to dispense its contents in a metered form; and

an ophthalmic solution therein, as hereinabove defined.

Finally, certain of the compounds represented by the above formula, disclosed below and utilized in the method of the present invention are novel and unobvious.

BRIEF DESCRIPTION OF THE DRAWING FIGURES

FIG. 1 is a schematic of the chemical synthesis of certain 1-carboxylic acid compounds of the invention specifically disclosed as Example 4(a)–(v) below.

FIG. 2 is a schematic of the chemical synthesis of certain δ-substituted thienyl 1-carboxylic acid compound of the invention specifically disclosed as Examples 6 and 6(a), below.
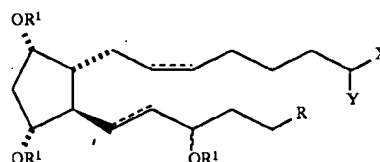
FIG. 3 is a schematic of the chemical synthesis of certain 1-amido compounds of the invention specifically disclosed as Examples 8(p)–(q), below.

FIG. 4 is a schematic of the chemical synthesis of certain δ-substituted thienyl 1-carboxylic acid compounds.

FIG. 5 is a schematic of the chemical synthesis of δ-substituted furanyl-1-carboxylic acid compounds specifically disclosed as Example 15.
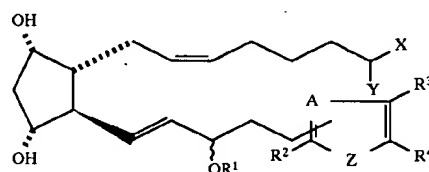
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DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to the use of nonacidic cyclopentane heptan(ene)oic acid, 2-heteroaryl alkenyl derivatives as therapeutic agents, e.g. as ocular hypotensives. The compounds used in accordance with the present invention are encompassed by the following structural formula I:
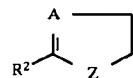

wherein the substituents and symbols are as hereinabove defined. The dotted lines on bonds between carbons 5 and 6 (C-5) and carbons 13 and 14 (C-13) indicate a single or double bond. If two solid lines are used at C-5, or C-13, it indicates a specific configuration for that double bond. Hatched lines used at position C-8, C-9 and C-11 indicate the α configuration. A triangle at position C-12 represents β orientation

A preferred group of the compounds of the present invention includes compounds that have the following structural formula II:

wherein Z is selected from the group consisting of O and S, A is selected from the group consisting of N, —CH, and C, R^2 is selected from the group consisting of hydrogen, halogen, and lower alkyl having from 1 to 6 carbon atoms, R^3 and R^4 are selected from the group consisting of hydrogen, halogen, lower alkyl having from 1 to 6 carbon atoms, or, together with
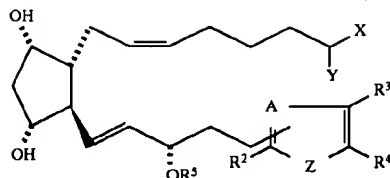

R^3 and R^4 forms a condensed aryl ring. Preferably, when X is $-N(R^1)_2$, Y is $=O$.

More preferably, at least one of R^2, R^3 or R^4 are independently selected from the group consisting of chloro, bromo and lower alkyl. In one aspect of the invention, at least one of R^2, R^3 or R^4 is chloro or bromo, and more preferably at least one of R^2, R^3 or R^4 is bromo or at least two of R^2, R^3 or R^4 are chloro. In another aspect of this invention, at least one of R^2, R^3 or R^4 is ethyl, propyl, or butyl.

Another preferred group includes compounds having the formula III:

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In the above formulae, the substituents and symbols are as hereinabove defined and R⁵ is hydrogen or methyl.

The above compounds of the present invention may be prepared by methods that are known in the art or according to the working examples below. The compounds, below, are especially preferred representative of the compounds of the present invention.

7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(3-(2-methyl)-thienyl-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid

7-[3α,5α,-Dihydroxy-2-(3α-hydroxy-5-(4-(2-methyl)-thienyl-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid

7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(2-(5-methyl)thienyl)-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(3-(2-chloro)thienyl)-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(2-(4-bromo)thienyl)-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(2-(5-bromo)thienyl)-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(3-(2,5-dichloro)thienyl)-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(2-(3-chloro)thienyl)-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(2-benzothienyl)-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(2-benzofuranyl)-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid

7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(2-(3-furanyl)-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(2-furanyl)-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(2-thiazolyl)-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(2-(thienyl)-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

7-[3α,5α-Dihydroxy-2-(3β-hydroxy-5-(2-thienyl)-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(3-thienyl)-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(3-(2,5-dichloro)thienyl-1E-pentenyl)cyclopentyl]-5Z-heptenamide.

7-[3α,5α-Dihydroxy-2-(3β-hydroxy-5-(3-thienyl)-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(3-thienyl)-1E-pentyl)cyclopentyl]-5Z-heptenoic acid.

7-[3α,5α-Dihydroxy-2-(3α-methoxy-5-(3-thienyl)-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(3-thienyl)-1E-pentenyl)cyclopentyl]-5Z-heptenamide.

7-[3α,5α-Dihydroxy-2-(3β-hydroxy-5-(3-thienyl)-1E-pentenyl)cyclopentyl]-5Z-heptenamide.

A pharmaceutically acceptable salt is any salt which retains the activity of the parent compound and does not impart any deleterious or undesirable effect on the subject to whom it is administered and in the context in which it is administered. Of particular interest are salts formed with inorganic ions, such as sodium, potassium, calcium, magnesium and zinc.

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Pharmaceutical compositions may be prepared by combining a therapeutically effective amount of at least one compound according to the present invention, or a pharmaceutically acceptable acid addition salt thereof, as an active ingredient, with conventional ophthalmically acceptable pharmaceutical excipients, and by preparation of unit dosage forms suitable for topical ocular use. The therapeutically efficient amount typically is between about 0.0001 and about 5% (w/v), preferably about 0.001 to about 1.0% (w/v) in liquid formulations.

For ophthalmic application, preferably solutions are prepared using a physiological saline solution as a major vehicle. The pH of such ophthalmic solutions should preferably be maintained between 6.5 and 7.2 with an appropriate buffer system. The formulations may also contain conventional, pharmaceutically acceptable preservatives, stabilizers and surfactants.

Preferred preservatives that may be used in the pharmaceutical compositions of the present invention include, but are not limited to, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate and phenylmercuric nitrate. A preferred surfactant is, for example, Tween 80. Likewise, various preferred vehicles may be used in the ophthalmic preparations of the present invention. These vehicles include, but are not limited to, polyvinyl alcohol, povidone, hydroxypropyl methyl cellulose, poloxamers, carboxymethyl cellulose, hydroxyethyl cellulose and purified water.

Tonicity adjustors may be added as needed or convenient. They include, but are not limited to, salts, particularly sodium chloride, potassium chloride, mannitol and glycerin, or any other suitable ophthalmically acceptable tonicity adjustor.

Various buffers and means for adjusting pH may be used so long as the resulting preparation is ophthalmically acceptable.

Accordingly, buffers include acetate buffers, citrate buffers, phosphate buffers and borate buffers. Acids or bases may be used to adjust the pH of these formulations as needed.

In a similar vein, an ophthalmically acceptable antioxidant for use in the present invention includes, but is not limited to, sodium metabisulfite, sodium thiosulfate, acetylcysteine, butylated hydroxyanisole and butylated hydroxytoluene.

Other excipient components which may be included in the ophthalmic preparations are chelating agents. The preferred chelating agent is edentate disodium, although other chelating agents may also be used in place or in conjunction with it.

The ingredients are usually used in the following amounts:

Ingredient	Amount (% w/v)
active ingredient	about 0.001–5
preservative	0–0.10
vehicle	0–40
tonicity adjustor	1–10
buffer	0.01–10
pH adjustor	q.s. pH 4.5–7.5
antioxidant	as needed
surfactant	as needed
purified water	as needed to make 100%

The actual dose of the active compounds of the present invention depends on the specific compound, and on the condition to be treated; the selection of the appropriate dose is well within the knowledge of the skilled artisan.

The ophthalmic formulations of the present invention are conveniently packaged in forms suitable for metered application, such as in containers equipped with a dropper, to facilitate the application to the eye. Containers suitable for dropwise application are usually made of suitable inert, non-toxic plastic material, and generally contain between about 0.5 and about 15 ml solution.

The invention is further illustrated by the following non-limiting Examples, which are summarized in the reaction schemes of FIGS. 1 through 4, wherein the compounds are identified by the same designator in both the Examples and the Figures.

Compound 4a

7-[3α,5α,-Dihydroxy-2-(3α-hydroxy-5-(3-(2-methyl) thienyl-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid

Step 1: Preparation of Enone 2a

To a suspension of sodium hydride (36 mg, 1.50 mmol) in THF (4.5 mL) cooled to 0° C. was added dimethyl 4-(3-(2-methyl) thienyl)-2-oxo-butylphosphonate(414 mg, 1.50 mmol) in THF (3.0 mL). After 0.25 h a solution of the aldehyde 1 (438 mg, 1.00 mmol) in THF (3.0 mL) was added and the reaction was allowed to slowly warm to 23° C. over a period of 8 h. The reaction solution was quenched with saturated aqueous NH₄Cl and extracted w/ EtOAc. The aqueous phase was made slightly acidic before extraction with EtOAc. The combined organics were washed with brine, dried (MgSO₄), filtered and concentrated in vacuo. Flash column chromatography (silica gel, 2:1 hex/EtOAc) gave 544 mg (93%) of the enone 2a.

Step 2: Preparation of alcohol 3a

Sodium tetrahydriodoborate (35 mg, 0.93 mmol) was added to a solution of the enone 2a (544 mg, 0.93 mmol) in MeOH(4.5 mL) at 0° C. After 2 h the solvent was removed in vacuo and the residue was stirred with 1N NaOH/EtOAc. The organic portion was separated, dried (MgSO₄), filtered and concentrated in vacuo. The 3a-alcohol was separated by flash column chromatography or HPLC (silica gel, 3:1 Hex/EtOAc).

Step 3: Preparation of 7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(3-(2-methyl)thienyl-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid

A solution of alcohol 3a and pyridinium p-toluene sulfonate (116 mg, 0.462 mmol) in MeOH(4.5 mL) was heated at 40° C. for 4 h. The solvent was removed in vacuo and the residue was diluted with EtOAc followed by washing with 1N HCl, saturated aqueous NaHCO₃ and brine. The organic portion was dried (MgSO₄), filtered and concentrated in vacuo.

The residue was diluted with THF (0.78 mL) and lithium hydroxide (0.39 mL of a 0.5N solution in H₂O, 0.194 mmol) was added. After 16 h the reaction was acidified with 1N HCl and extracted with EtOAc. The organic portion was washed with brine, dried (MgSO₄), and concentrated in vacuo to give 37.6 mg of the acid 4a.

The title compound was identified by the following NMR spectrum.

¹H NMR (300 MH₂, CDCl₃) δ12.1(brs, 1H), 6.98 (d,J=5.1 Hz), 6.81(d, J=5.1 Hz, 1H), 5.30–5.64(m, 4H), 4.92(brs, 3H), 4.07–4.17 (m, 2H), 3.89–3.93(m, 1H), 2.55–2.59 (m,2H), 2.35(δ,3H), 2.07–2.33(m,10H), 1.42–1.86(m,4H).

By methods described for compound 4a, steps 1 through 3, the following compounds were prepared. (The compounds below are also identified by their NMR spectra.)

Compound 4b

7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(2-(5-methyl) thienyl)-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

According to the procedures described above for 4a, the use of dimethyl 4-(2-(5-methyl)thienyl)-2-oxo-butylphosphonate afforded 26 mg of free acid 4b.

¹H NMR (300 MH₂, CDCl₃) δ12.1(brs, 1H), 6.56 (d,J=3.4 Hz, 1H), 6.54(d, J=3.4 Hz, 1H), 5.34–5.64(m, 4H), 4.70(brs, 3H), 4.13–4.20 (m, 2H), 3.91–3.93(m, 1H), 2.82 (t, J=7.7 Hz, 2H), 2.42(δ,3H), 2.05–2.38(m,11H), 1.44–1.96(m,5H).

Compound 4c

7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(3-(5-methyl) thienyl)-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

According to the procedures described above for 4a, the use of dimethyl 4-(3-(2-methyl)thienyl)-2-oxo-butyl phosphonate afforded 25 mg of free acid 4c.

¹H NMR (300 MH₂, CDCl₃) δ12.0(brs, 1H), 6.67 (s, 1H), ·6.60(s, 1H), 5.34–5.62(m, 4H), 4.42(brs, 3H), 4.10–4.17 (m, 2H), 3.89–3.93(m, 1H), 2.57–2.60(m, 2H), 2.44(δ,3H), 2.09–2.36(m, 8H), 1.44–1.87(m,6H).

Compound 4d

7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(3-(2-chloro) thienyl)-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

According to the procedures described above for 4a, the use of dimethyl 4-(3-(2-chloro)thienyl)-2-oxo-butylphosphonate afforded 25 mg of free acid 4d.

¹H NMR (300 MH₂, CDCl₃) δ12.0(brs, 1H), 6.99 (d, J=5.7H₂), 6.78(d, J=5.7 Hz,1H), 5.29–5.60(m, 4H), 4.02–4.11 (m, 2H), 3.84–3.87(m, 1H), 3.37(brs, 3H), 2.56–2.63(m, 2H), 2.01–2.32(m, 8H), 1.38–1.83(m,7H).

Compound 4e

7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(2-(4-bromo) thienyl)-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

According to the procedures described above for 4a, the use of dimethyl 4-(2-(4-bromo)thienyl)-2-oxo-butylphosphonate afforded 10 mg of free acid 4e.

¹H NMR (300 MH₂, CDCl₃) δ12.01(brs, 1H), 6.95 (s, 1H), 6.65(s, 1H), 5.24–5.53(m, 4H), 3.99–4.08 (m, 2H), 3.76–3.80(m, 1H), 2.70–2.79(m, 2.44(s,3H), 2.09–2.36(m, 8H), 1.44–1.87(m,6H).

Compound 4f

7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(2-(5-bromo) thienyl)-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

According to the procedures described above for 4a, the use of dimethyl 4-(2-(5-bromo)thienyl)-2-oxo-butylphosphonate afforded 50 mg of free acid 4f.

¹H NMR (300 MH₂, CDCl₃) δ12.0(brs, 1H), 6.80 (d, J=3.6 Hz, 1H), 6.51(d, J=3.9 Hz, 1H), 5.33–5.55(m, 4H), 4.05–4.12(m, 2H), 3.82–3.88(m, 1H), 2.75–2.81(m, 2H), 1.38–2.28 (m,14H).

Compound 4g

7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(3-(2,5-dichloro) thienyl)-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

According to the procedures described above for 4a, the use of dimethyl 4-(3-(2,5-dichloro)thienyl)-2-oxo-butylphosphonate afforded 18 mg of free acid 4g.

¹H NMR (300 MHz, CDCl₃) δ12.01(brs, 1H), 6.64 (s, 1H), 5.27–5.56(m, 4H), 4.05–4.15(m, 2H), 3.85–3.92(m, 1H),1.42–2.31(m,18H).

Compound 4 h

7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(2-(3-chloro) thienyl)-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

According to the procedures described above for 4a, the use of dimethyl 4-(2-(3-chloro)thienyl)-2-oxo-butylphosphonate afforded 10 mg of free acid 4 h.

¹H NMR (300 MHz, CDCl₃) δ12.0(brs, 1H), 7.13 (d, J=5.4 Hz, 1H), 6.75(d, J=5.4 Hz, 1H), 5.19–5.46(m, 4H), 3.96–3.98(m, 2H), 3.69–3.76(m, 1H), 2.75(m, 2H), 1.35–2.28(m, 17H).

Compound 4i

7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(2-benzothienyl)-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

According to the procedures described above for 4a, the use of dimethyl 4-(2-benzothienyl)-2-oxo-butylphosphonate afforded 22 mg of free acid 4i.

¹H NMR (300 MHz, CDCl₃) δ11.8(brs, 1H), 7.73(d, J=7.7 Hz, 1H), 7.63(d, J=6.9 Hz, 1H), 7.23–7.31(m, 2H), 7.00(s, 1H), 5.31–5.65(m, 4H), 4.86(brs, 3H), 4.16–4.22 (m, 2H), 3.89–3.93(m, 1H), 2.96 (t, J=7.6 Hz, 2H)1.86–10H), 1.44–1.78(m, 4H).

Compound 4j

7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(2-benzofuranyl)-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

According to the procedures described above for 4a, the use of dimethyl 4-(2-benzofuranyl)-2-oxo-butylphosphonate afforded 30.5 mg of free acid 4j.

¹H NMR (300 MHz, CDCl₃) δ12.1(brs, 1H), 7.37–7.47 (m, 2H), 7.15–7.19(m, 2H), 6.38(s, 1H),5.30–5.66 (m, 4H), 5.04 (brs, 3H), 4.10–4.20(m, 2H), 3.86–3.94(m, 1H), 2.84(t, J=7.6 Hz, 2H)1.90–2.33(m, 10H), 1.38–1.78(m,4H).

Compound 4k

7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(2-(3-furanyl)-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

According to the procedures described above for 4a, the use of dimethyl 4-(3-furanyl)-2-oxo-butylphosphonate afforded 10.1 mg of free acid 4k.

¹H NMR (300 MH₂, CDCl₃) δ12.0(brs, 1H), 7.35 (d, J=1.7 Hz, 1H), 7.23(s, 1H), 6.28 (d, J=1.7 Hz, 1H), 5.34–5.64(m, 4H), 4.15–4.20(m, 2H), 3.90–3.94 (m, 1H), 3.70 (brs, 3H), 2.09–2.52 (m, 12H), 1.40–1.88 (m, 4H).

Compound 4l

7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(2-furanyl)-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

According to the procedures described above for 4a, the use of dimethyl 4-(2-furanyl)-2-oxo-butylphosphonate afforded 33.3 mg of free acid 4l.

¹H NMR (300 MHz, CDCl₃) δ11.8(brs, 1H), 7.29(s, 1H), (d, J=3.0 Hz 1H), 6.26(dd, J=3.0, 1.8 Hz, 1H), 5.99 (d, J=1.8 Hz, 1H) 5.34–5.64 (m, 4H), 4.82 (brs, 3H), 4.11–4.17 (m, 2H), 3.89–3.93 (m, 1H), 2.69 (t, J=8.4 Hz, 2H), 2.05–2.34 (m, 10H), 1.40–1.94(m, 4H).

Compound 4m

7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(2-thiazolyl)-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

According to the procedures described above for 4a, the use of dimethyl 4-(2-thiazolyl)-2-oxo-butylphosphonate afforded 32.2 mg of free acid 4m.

¹H NMR (300 MHz, CD₃OD) δ7.47 (d, J=3.3 Hz, 1H), 7.23(d, J=3.3 Hz, 1H), 3.86–3.93 (m,2H), 3.60–3.65 (m, 1H), 2.88–2.95 (m, 2H), 1.75–2.20 (m, 10H), 1.22–1.44(m, 4H).

Compound 4n

7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(2-(thienyl)-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

According to the procedures described above for 4a, the use of dimethyl 4-(2-thienyl)-2-oxo-butylphosphonate afforded 15.0 mg of free acid 4n.

¹H NMR (300 MHz, CDCl₃) δ11.9(brs, 1H), 7.11, (d, J=5.1 Hz, 1H), 6.92(dd, J=5.1, 3.3 Hz, 1H), 6.00 (d, J=3.3 Hz, 1H) 5.32–5.64 (m,4H), 4.15–4.19(m, 2H), 3.93–3.97 (m, 1H), 3.61 (brs, 3H), 2.89–2.95 (m, 2H), 2.09–2.35 (m, 8H), 1.46–1.98(m, 6H).

Compound 4o

7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(2-thienyl)-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

The 3β-isomer of 3n was isolated from the reaction mixture obtained in step 2 during preparation of 4n and subjected to step 3 to afford 14.3 mg of free acid 4o.

¹H NMR (300 MHz, CDCl₃) δ11.5(brs, 1H), 7.11, (d, J=5.1 Hz 1H), 6.92(dd, J=5.1, 3.3 Hz, 1H), 6.81 (d, J=3.3 Hz, 1H) 5.36–5.64 (m, 4H), 4.62 (brs, 3H), 4.17–4.21 (m, 2H), 3.95–3.98 (m, 1H), 2.90–2.96 (m, 2H), 2.08–2.34 (m, 8H), 1.40–1.98(m, 6H).

Compound 4p

7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(3-thienyl)-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

According to the procedures described above for 4a, the use of dimethyl 4-(3-thienyl)-2-oxo-butylphosphonate afforded 9.6 mg of free acid 4p. While this compound is not a substituted heteroaryl derivative within the scope of general Formula I, above, it represents another aspect of this invention in view of its excellent ability to lower intraocular pressure as shown below.

¹H NMR (300 MHz, CDCl₃) δ12.0(brs, 1H), 7.23–7.27 (m, 1H), 6.94–6.95 (m, 2H), 5.36–5.65 (m, 4H), 4.10–4.17 (m, 2H), 3.94 (brs, 3H), 3.90–3.94 m, 1H), 2.68–2.74 (m, 2H), 2.00–2.35 (m, 8H), 1.44–1.96(m, 6H).

Compound 4q

7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(3-thienyl)-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

The 3β-isomer of 3p was isolated from the reaction mixture obtained in step 2 during preparation of 4p and subjected to step 3 to afford 36.2 mg of free acid 4q.

¹H NMR (300 MHz, CDCl₃) δ11.9(brs, 1H), 7.23–7.27 (m, 1H), 6.94–6.95 (m, 2H), 5.32–5.65 (m, 4H), 4.72 (brs, 3H), 4.12–4.19 (m, 2H), 3.93–3.97 (m, 1H), 2.69–2.76 (m, 2H), 2.07–2.33(m, 8H), 1.39–1.90 (m, 6H).

Compound 4r

7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(2-(5-ethyl)thienyl-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

According to the procedures described above for 4a, the use of dimethyl ⁴-(2(5-ethyl)thienyl)2-oxo-butylphosphonate will result in the free acid 4r.

Compound 4s

7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(2-(5-butyl)thienyl-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

According to the procedures described above for 4a, the use of dimethyl 4-(²-(5-butyl)thienyl)2-oxo-butylphosphonate will result in the free acid 4s.

Compound 4t

7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(2-(5-propyl) thienyl-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

According to the procedures described above for 4a, the use of dimethyl 4-(2-(5-propyl)thienyl)2-oxo-butylphosphonate will result in the free acid 4t.

Compound 4u

7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(2-(5-methoxy) thienyl-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

According to the procedures described above for 4a, the use of dimethyl 4-(2-(5-methoxy)thienyl)2-oxo-butylphosphonate will result in the free acid 4u.

Compound 4v

7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(2-thiazolyl)-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

The 3β isomer of 3m was isolated from the reaction mixture obtained in Step 2 during preparation of 4m and subjected to Step 3 to afford the free acid 4v.

Compound 4w

7-[3α,5α-Dihydroxy-2-(3-hydroxy-5-(2-(3-chloro)thienyl)-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

Compound 6

7-[3α,5α-Dihydroxy-2-(3-methoxy-5-(3-thienyl)-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

Alcohol (400 mg, 0.694 mmol) obtained in step 2 of preparation of 4p was treated with silver triflate (803 mg, 3.12 mmol), 2,6-di-t-butyl-pyridine (0.89 mL, 3.98 mmol) and iodomethane (0.21 mL, 3.4 mmol) in CH₂Cl₂ (11 mL) at 0° C. After 12 h the reaction mixture was filtered through celite, concentrated in vacuo and purified by flash column chromatography to give the 3α-methoxy product 5. Further

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subjection of 5 to the procedures described above in step 3 of preparation of 4a provided 41.2 mg of free acid 6.

^{1}H NMR (300 MHz, CDCl$_3$) δ11.6(brs, 1H), 7.24–7.28 (m, 2H), 6.93 (d, J=3.3 Hz, 1H), 5.34–5.60 (m,4H), 4.90 (brs, 3H), 4.20–4.23 (m,1H), 3.99–4.02(m, 1H), 3.54–3.64 (m, 1H), 3.30 (s, 3H), 2.69 (t, J=7.3 Hz, 2H), 2.07–2.42 (m, 9H), 1.50–2.01 (m, 5H).

Compound 6a

7-[3α,5α-Dihydroxy-2-(3-hydroxy-5-(2-(3-chloro)thienyl)-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

The racemate of the alcohol prepared according to step 2 of preparation 4 h is treated according to the procedures described above for 6 and results in the free acid 6a.

Compound 8p

7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(3-thienyl)-1E-pentenyl)cyclopentyl]-5Z-heptenamide.

The 3α-alcohol 3p, isolated from step 2 during preparation of 4p, was deprotected with pyridinium p-toluenesulfonate in MeOH at 45° C. for 4 h and after the usual work-up gave triol 7p.

A mixture of 7p and ammonium chloride in liquid ammonia was heated to 55° C. for 48 h in a sealed tube. The tube was recooled to –70° C., vented, and then allowed to warm to room temperature on its own accord. The residue was dissolved in 1:1 EtOAc/H$_2$O. The organic portion was separated, dried (MgSO$_4$), filtered and concentrated in vacuo. Flash column chromatography (silica gel, 9:1 CH$_2$Cl$_2$/MeOH) gave 10.9 mg of the title compound 8p.

^{1}H NMR (300 MHz, CDCl$_3$) δ7.24–7.27(m, 1H), 6.95–6.96 (m, 2H), 5.76 (brs, 1H), 5.34–5.63 (m, 4H), 4.08–4.19 (m, 2H), 3.94–3.98(m, 1H), 2.95 (brs, 3H), 2.69–2.76 (m, 2H), 2.05–2.39 (m, 8H), 1.48–1.96 (m, 6H).

Compound 8q

7-[3α,5α-Dihydroxy-2-(3β-hydroxy-5-(3-thienyl)-1E-pentenyl)cyclopentyl]-5Z-heptenamide.

According to the procedures described for preparation of 8p the 3β-alcohol 3 g was converted to the title compound 8q.

^{1}H NMR (300 MHz, CDCl$_3$) δ7.24–7.27 (m, 1H) 6.95–6.97 (m, 2H), 5.72(brs, 2H), 5.34–5.66 (m, 4H), 4.08–4.19 (m, 2H), 3.95–3.99 (m, 1H), 3.04 (brs, 1H), 2.70–2.84 (m, 4H), 2.08–2.36 (m, 9H), 1.42–1.89 (m, 5H).

Compound 8r

7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(3-(2,5-dichloro) thienyl)-1E-pentenyl)cyclopentyl]-5Z-heptenamide.

According to the procedures described for preparation of 8p the alcohol 3r was converted to the title compound 8r.

^{1}H NMR (300 MHz, CDCl$_3$) δ6.64 (s, 1H), 5.26–5.68 (m, 6H), 4.07–4.10 (m, 1H), 3.97–4.03 (m,1H), 3.83–3.86 (m, 1H), 2.50–2.56 (m, 2H), 1.96–2.30(m, 11H), 1.39–1.80(m, 6H).

Compound 13

7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(3-thienyl)pentyl) cyclopentyl]-5Z-heptenoic acid.

Step 1: Preparation of Alcohol

To a suspension of sodium hydride 271 mg (11.30 mmol) in THF (21 mL) cooled to 0° C. was added a solution of dimethyl 4-(3-thienyl)-2-oxo-butylphosphonate (2.96 g, 11.30 mmol) in THF (10 mL). After stirring for 0.5 h a solution of aldehyde 9 (2.80 g, 10.28 mmol) in THF (10 mL) was added dropwise. The reaction was allowed to warm to room temperature and stirred for a total of 12 h before quenching with saturated aqueous NH$_4$Cl. The mixture was extracted with EtOAc and the organic portion was washed with saturated aqueous NaHCO$_3$, brine, dried (MgSO$_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 1:1 hex/EtOAc) to afford 3.98, (95%) of enone.

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Immediately, a solution of the enone (3.98 g, 9.75 mmol) in MeOH (22 mL) was cooled to 0° C. and sodium tetrahydridoborate (369 mg, 9.75 mmol) was added. After 2 h the reaction was quenched with saturated aqueous NH$_4$Cl and extracted with EtOAc. The organic portion was washed with brine, dried (MgSO$_4$) filtered and concentrated in vacuo. Purification by HPLC (Waters Partisil-10, 1:1 hex/EtOAc) afforded 1.30 g (33%) of the α-alcohol 10.

^{1}H NMR (300 MHz, CDCl$_3$) δ7.97 (d, J=7.2 Hz, 2H), 7.21–7.57, (m, 4H), 6.88 (d,J=4.1 Hz, 2H), 5.54–5.70 (m, 2H), 5.23 (q, J=6.1 Hz, 1H), 5.04 (t, J=6.5 Hz, 1H), 4.10 (q, J=7.1 Hz 1H), 2.45–2.89 (m, 7H), 2.18–2.26 (m,2H), 1.76–1.84 (m, 2H).

Step 2: Preparation of Bis-Silyl ether 11

Potassium carbonate (523 mg, 3.78 mmol) was added to a solution of benzoate 10 (1.3 g, 3.15 mmol) in MeOH(6.5 mL). After 16 h the reaction solvent was removed in vacuo and the residue was dissolved in EtOAc/saturated aqueous NH$_4$Cl. The organic portion was washed with brine, dried (MgSO$_4$), filtered and concentrated in vacuo.

The residue was dissolved in THF (6.5 mL) and triphenylphosphine rhodium chloride (400 mg) was added. The solution was degassed and purged under an atmosphere of hydrogen gas at 40–45 psi. After 16 h the reaction was concentrated in vacuo, and the residue purified by flash column chromatography (silica gel, 3:1 hex/EtOAc) to afford the apparent saturated diol after evaporation of the solvents.

The apparent diol was dissolved in CH$_2$Cl$_2$ (6.5 mL) and 2,6-lutidine (2.0 mL, 16.5 mmol) was added followed by t-butyldimethylsilyl triflate (3.0 mL, 13.2 mmol). The reaction was quenched with saturated aqueous NaHCO$_3$ and washed with brine, dried (MgSO$_4$), filtered and concentrated in vacuo. Flash column chromatography (9:1 hex/EtOAc) gave 1.29 g (94%) of the bis-TBDMS ether 11.

Compound 11

^{1}H NMR (300 MHz, CDCl$_3$) δ7.22–7.25 (m, 1H), 7.22–7.23 (m, 2H), 4.92–4.98 (m, 1H), 3.90–3.94 (m, 1H), 3.64–3.70 (m, 1H), 2.45–2.82 (m, 5H), 1.95–2.16 (m, 2H), 1.71–1.77 (m, 3H), 1.05–1.51 (m, 4H), 0.88 (s, 9H), 0.85 (s, 9H), 0.03 (s, 9H), 0.02 (s, 3H).

Step 3: Preparation of ester 12

Lactone 11 (170 mg, 0.315 mmol) was dissolved in CH$_2$Cl$_2$ (1.0 mL) and cooled to –70° C. Dibal-H(0.47 mL of a 1.0M solution in CH$_2$Cl$_2$, 0.47 mmol) was added. After 2 h the reaction was quenched with MeOH, allowed to warm to room temperature, and extracted with CH$_2$Cl$_2$. The organic portion was dried (Na$_2$SO$_4$), filtered and concentrated in vacuo to give the lactol as a clear, viscous oil.

To a suspension of (4-carboxybutyl) triphenylphosphonium bromide (558 mg, 1.26 mmol) in THF (2.5 mL) was added potassium bis (trimethylsilyl) amide(503 mg, 2.52 mmol) at 0° C. After 0.5 h the solution was cooled to –70° C. and a solution of the lactol in THF (2.5 mL) was added. The reaction was allowed to warm to room temperature on its own accord, quenched with saturated aqueous NH$_4$Cl, and extracted with EtOAc. The organic portion was washed with saturated aqueous NaHCO$_3$, brine, dried (MgSO$_4$), filtered and concentrated in vacuo. The residue was diluted with Et$_2$O and excess diazomethane in Et$_2$O was added until the reaction solution persisted yellow. Evaporation of the solvent gave 140 mg (70%) of ester 12.

^{1}H NMR (300 MHz, CDCl$_3$) δ7.22–7.24 (m, 1H), 6.90–6.92 (m, 2H), 5.28–5.52 (m, 2H), 4.02–4.06 (m, 1H), 3.95–3.96 (m, 1H), 3.63–3.67 (m, 1H), 3.63 (s, 3H), 2.52–2.70 (m, 2H), 2.00–2.32 (m, 5H), 1.20–1.84 (m, 14H),

0.88 (s, 9H), 0.86 (s, 9H), 0.108–0.055 (m, 12H), (d, J=7.2 Hz, 2H), 7.21–7.57, (m, 4H), 6.88 (d,J=4.1 Hz, 2H), 5.54–5.70 (m, 2H), 5.23 (q, J=6.1 Hz, 1H), 5.4 (+, J=6.5 Hz, 1H), 4.10 (q, J-7.1 Hz 1H), 2.45–2.89 (m, 7H), 2.18–2.26 (m, 2H), 1.76–1.84 (m, 2H).

Step 4: Preparation carboxylic acid 13

To a solution of bis-TBDMS ether 12 (25 mg, 0.040 mmol) in THF (0.24 mL) was added Bu$_4$NF (0.12 mL of a 1.0M solution in THF, 0.12 mmol). After 16 h the reaction was concentrated in vacuo and purified by flash column chromatography (silica gel, 3:1 hex/EtOAc) to yield 13.0 mg (79%) of the triol.

Lithium hydroxide (0.15 mL of a 0.5N solution in H$_2$O, 0.073 mmol) was added to a solution of the ester (13.0 mg, 0.0316 mmol) in THF (0.3 mL). After 16 h the reaction was acidified with 1N HCl and extracted with EtOAc. The organic portion was dried (MgSO$_4$), filtered and concentrated in vacuo to give 7.0 mg (56%) of free acid 13.

^{1}H NMR (300 MHz, CDCl$_3$) δ12.0 (brs, 1H), 7.19–7.22 (m, 1H), 6.90–6.92 (m, 2H), 5.31–5.48 (m, 2H), 4.10 (+, J=3.9 Hz, 1H), 3.86–3.88 (m, 1H), 3.59–3.65 (m, 1H), 2.65–2.82 (m, 2H), 1.20–2.30 (m, 21H).

Compound 15

7-[3α,5α-Dihydroxy-2-(3-hydroxy-5-(3-furanyl)pentyl) cyclopentyl]-5Z-heptenoic acid 15.

Step 1: Preparation of ketone 14

A mixture of the enone (137 mg, 0.245 mmol) obtained in step 2 of preparation of 4k above, Aliquat 336 (34 μL, 0.074 mmol), sodium dithionite (384.7 mg, 2.21 mmol) and sodium bicarbonate (371.3 mg, 4.42 mmol) in benzene: H$_2$O (1:1, 6.0 mL) was heated to 75° C. for 1.5 h. The reaction mixture was allowed to cool to room temperature, was diluted with EtoAc, and was washed with H$_2$O and brine. The organic portion was dried (MgSO$_4$), filtered and the filtrate was concentrated in vacuo. Purification by flash column chromatography (silica gel, 4:1 hex/EtOAc) gave 113.3 mg (83%) of the ketone 14.

Step 2: Preparation of 7-[3α,5α-Dihydroxy-2-(3-hydroxy-5-(3-furanyl)pentyl) cyclopentyl]-5Z-heptenoic acid 15

Sodium tetrahydridoborate (14.2 mg, 0.375 mmol) was added to a solution of the ketone (210 mg, 0.375 mmol) in MeOH (3.0 mL) cooled to 0° C. After 30 minutes the reaction was quenched with saturated aqueous ammonium chloride and allowed to warm to room temperature. The mixture was extracted with Et$_2$O and the organic portion was dried (MgSO$_4$), filtered and concentrated in vacuo.

The residue was diluted with MeOH (3.0 mL) and pyridinium p-toluene sulfonate (141 mg, 0.562 mmol) was added. After heating to 45° C. for 16 h the reaction was concentrated in vacuo, diluted with EtOAc and washed with 1N HCl, saturated aqueous sodium bicarbonate, brine, dried (MgSO$_4$), filtered and concentrated in vacuo. Flash column chromatography (silica gel, 2:1 hex/EtOAc) followed by 100% EtOAc) gave 123 mg (83%) of a mixture of alcohols which were homogenous by TLC.

The mixture of alcohols (52.3 mg, 0.132 mmol) was diluted with THF (1.0 mL) and lithium hydroxide (0.53 mL of a 0.5N solution in H$_2$O, 0.265 mmol) was added. After 16 h the reaction was acidified with 1N HCl and extracted with EtOAc. The organic portion was washed with brine, dried (MgSO$_4$) filtered and concentrated in vacuo to afford 44.6 mg (89%) of free acid 15.

^{1}H NMR (300 MHz, CDCl$_3$) δ7.34 (d, J=1.8 Hz, 1H), 7.23 (s, 1H), 6.2 (d, J=1.8 Hz, 1H), 5.30–5.52 (m, 2H), 4.81 (brs, 3H) 4.16 (brs, 1H), 3.95 (brs, 1H), 3.61–3.72 (m, 1H), 2.10–2.64 (m, 7H), 2.17 (s, 3H), 1.34–1.91 (m, 10H).

Certain of the above compounds were tested for activity in the various in vitro assays described below and the results are reported in Tables 1 through 4, below.

Activity at different prostanoid receptors was measured in vitro in isolated smooth muscle preparations. FP-activity was measured as contraction of the isolated feline iris sphincter. EP$_1$-activity was measured as contraction of the longitudinal smooth muscle of the isolated guinea pig ileum. EP$_3$-activity was measured as inhibition of the twitch response induced by electrical field stimulation in the isolated guinea pig was deferens and as contraction of the longitudinal smooth muscle of the isolated chick ileum. Activity was also measured as relaxation of smooth muscle of isolated rabbit jugular vein a preparation which appears to contain a unique PGF$_{2α}$-sensitive receptor provisionally termed FP$_{VASC}$. TP-vasoconstrictor activity was measured as contraction of rings of the isolated rat thoracic aorta. Effects on platelets from healthy human donors were measured by incubating platelet-rich plasma with the compounds described herein. Inhibition of aggregation was determined by the ability of the compounds described herein to inhibit platelet aggregation in platelet-rich plasma induced by 20 μM ADP.

In addition to stimulating the FP receptor associated with the cat iris, several examples also stimulated the EP$_3$ receptor. Compounds with agonist activity at EP$_3$ receptors may also be used for treating gastric or duodenal ulcer by virtue of their cytoprotective and anti-secretory properties. They may also be used as adjunctive therapy in combination with aspirin-like drugs and steroids to limit gastrointestinal side effects. EP$_3$ agonists stimulate uterine smooth muscle and may be used to terminate pregnancy in human females. EP$_3$ agonists are also useful in the cervical ripening process and could be used for inducing labor.

Other potential therapeutic applications are in osteoporosis, constipation, renal disorders, sexual dysfunction, baldness, diabetes, cancer and in disorder of immune regulation.

Many examples also have pronounced activity at the FP receptor, provisionally termed FP$_{VASC}$ associated with the vascular endothelium in the rabbit jugular vein preparation. Since such agents would be vasodilators they have potential in hypertension and any disease where tissue blood perfusion is compromised. Such indications include, but are not limited to, systemic hypertension, angina, stroke, retinal vascular diseases, claudication, Raynauds disease, diabetes, and pulmonary hypertension.
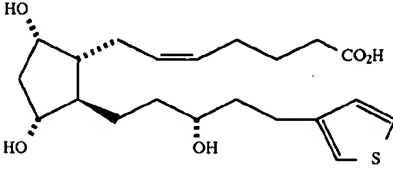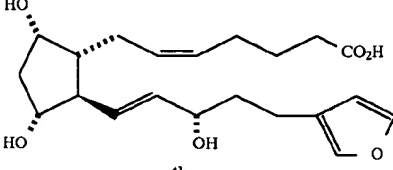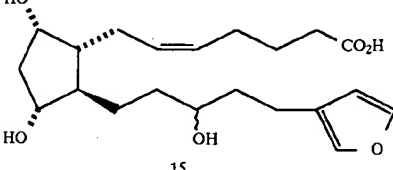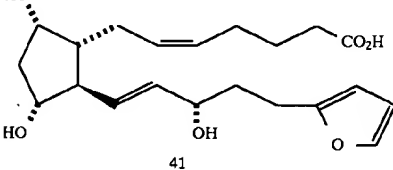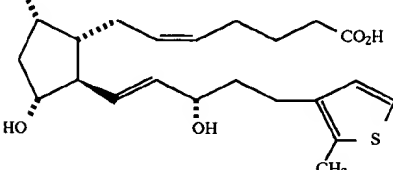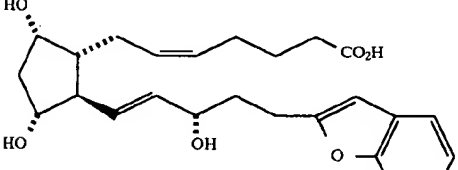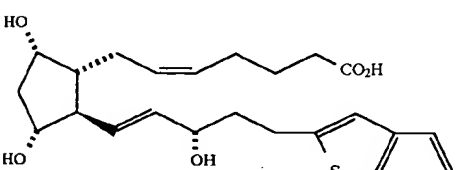
The effects of the compounds of this invention on intraocular pressure are also provided in the following tables. The compounds were prepared at the said concentrations in a vehicle comprising 0.1% polysorbate 80 and 10 mM TRIS base. Dogs were treated by administering 25 μl to the ocular surface, the contralateral eye received vehicle as a control. Intraocular pressure was measured by applanation pneumatonometry. Dog intraocular pressure was measured immediately before drug administration and at 6 hours thereafter.

Compound 4 g was examined and showed a pronounced ocular hypotensive effect in dogs.
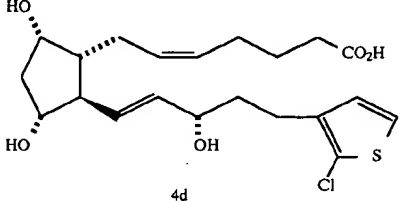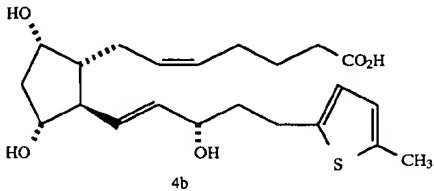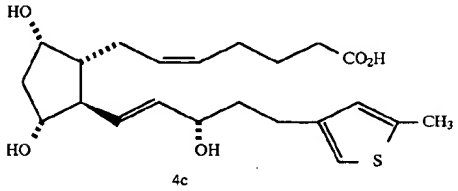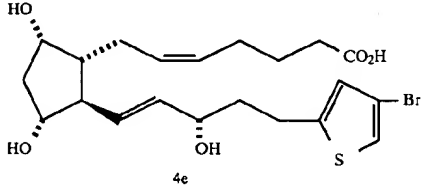
AGN-#	EC$_{50}$ (nM)					Platelets		Dog IOP	Hyp/
	FP	EP$_1$	EP$_3$	FP$_{VASC}$	TP	aggreg	inhib	(1 day)	Miosis
4e	4.2	>10^4	43 p.a. 1230	20	4010	NA	NA	0.1%/-2.8	0.38/ pinpt
4o	82	>10^4	>10^4 1820	31	>10^4			0.1%/-4.2	0.79/ pinpt
4p	0.8	2000	400 178	9.2	2460	NA	NA	0.1%/-6.0	0.6/ pinpoint
8p	3.5	>10^4	>10^4 5000	3.6	>10^4				
4q	30		58						
8q	170							0.1%/-3.3	0.72*/ pin
6	0.8	>10^{4}pa	189pa 1060	2.1	~10^4	NA	NA	0.1%/-2.1	0.83/ pinpt

-continued

| AGN-# | EC$_{50}$ (nM) | | | | | Platelets | | Dog IOP | Hyp/ |
	FP	EP$_1$	EP$_3$	FP$_{VASC}$	TP	aggreg	inhib	(1 day)	Miosis
13	10	>10^4	105pa 2400	545	4740	NA	NA		
4k	19	>10^4	83 2510		5400			0.1%/−3.6 0.01%/ −2.5	0.38/ pinpoint 0.83/ mild
15	137			>5882					
41	9	>10^4	44 1150	>7692	~10^4			0.1%/−4.3 0.01%/ −1.7	0.67/ pinpoint 0.54/ mild
4a	12	>10^4	355 3470	>833	3980				
4j	190		9000pa	>68966				0.1%/0 0.01%/ −1.2	0.13/0 0.17/0
4i	291		~10^4	2664					

-continued

AGN-#		EC$_{50}$ (nM)					Platelets		Dog IOP	Hyp/
		FP	EP$_1$	EP$_3$	FP$_{VASC}$	TP	aggreg	inhib	(1 day)	Miosis
4d		4	>10^4	1000pa 6170	47	2450			0.1%/−3.3	1.13/ pinpoint
4b		7	>10^4	341 pa 8710	>7692	>10^4				
4c		3	>10^4	305 pa 2040	>7143	~10^4			0.1%/−4.5 0.01%/ −2.9	1.38/ pinpt 0.42/ pinpt
4e		0.8	>10^4	50 pa 2190	16	371				
4g		0.49	>10^4	>10^{4}pa >10^4	7.7	2300			0.1%/−5.6	0.5/ pinpt
4f		4	>10^4	36pa 7410	8.5	5080			0.1%/−4.8	1.0/ pinpoint
4m		503			1003				0.1%/−3.2	0.6/ pinpoint

-continued

| AGN-# | EC$_{50}$ (nM) | | | | | Platelets | Dog IOP | Hyp/ |
	FP	EP$_1$	EP$_3$	FP$_{VASC}$	TP	aggreg inhib	(1 day)	Miosis
4v	4230			28325				
4h	13	>10^4 >10^4	=10^{4}pa	122	3530			
4r	33			21	>10^4			
4u	202							
4s	2940							
4t	53							
8r	0.70	NA		82	>10^4	0.1%/−5.8		1.2/ pinpoint

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The compounds of the invention may also be useful in the treatment of various pathophysiological diseases including acute myocardial infarction, vascular thrombosis, hypertension, pulmonary hypertension, ischemic heart disease, congestive heat failure, and angina pectoris, in which case the compounds may be administered by any means that effect vasodilation and thereby relieve the symptoms of the disease. For example, administration may be by oral, transdermal, parenterial, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, or buccal routes.

The compounds of the invention may be used alone, or in combination with other of the known vasodilator drugs.

The compounds of the invention may be formulated into an ointment containing about 0.10 to 10% of the active ingredient in a suitable base of, for example, white petrolatum, mineral oil and petrolatum and lanolin alcohol. Other suitable bases will be readily apparent to those skilled in the art.

The pharmaceutical preparations of the present invention are manufactured in a manner which is itself known, for example, by means of conventional dissolving or suspending the compounds, which are all either water soluble or suspendable. For administration in the treatment of the other mentioned pathophysiological disorders. The pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer such as glycerol or sorbitol. The push-fit capsules can contain the active compounds in liquid form that may be mixed with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds are preferably dissolved or suspended in suitable liquids, such as in buffered salt solution. In addition, stabilizers may be added.

In addition to being provided in a liquid form, for example in gelatin capsule or other suitable vehicle, the pharmaceutical preparations may contain suitable excipients to facilitate the processing of the active compounds into preparations that can be used pharmaceutically. Thus, pharmaceutical preparations for oral use can be obtained by adhering the solution of the active compounds to a solid support, optionally grinding the resulting mixture and processing the mixture of granules, after adding suitable auxiliaries, if desired or necessary, to obtain tablets or dragee cores.

Suitable excipients are, in particular, fillers such as sugars, for example lactose or sucrose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, as well as inders such as starch, paste using for example, maize starch, wheat starch, rich starch potato starch, gelatin, tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinyl pyrrolidone. If desired, disintegrating agents may be added such as the above-mentioned starches and also carboxymethyl-starch, crosslinked polyvinyl pyrrolidone, agar, or algenic acid or a salt thereof, such as sodium alginate. Auxiliaries are, above all, flow-regulating agents and lubricants, for example, silica, talc, stearic acid or salts thereof, such as magnesium stearate or calcium stearate, and/or polyethylene glycol. Dragee cores are provided with suitable coatings which if desired, are resistant to gastric juices. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. In

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order to produce coatings resistant to gastric juices, solutions of suitable cellulose preparations such as acetylcellulose phthalate or hydroxypropylmethyl-cellulose phthalate, are used. Dye stuffs or pigments may be added to the tablets or dragee coatings, for example, for identification or in order to characterize combinations of active compound doses.
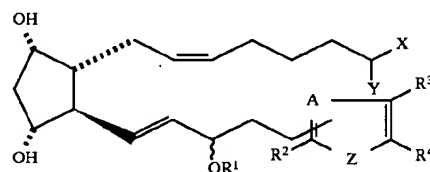
Suitable formulations for intravenous or parenteral administration include aqueous solutions of the active compounds.

In addition, suspensions of the active compounds as oily injection suspensions may be administered. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension include, for example, sodium carboxymethyl cellulose, soribitol, and/or dextran. Optionally, the suspension may also contain stabilizers.

The foregoing description details specific methods and compositions that can be employed to practice the present invention, and represents the best mode contemplated. However, it is apparent for one of ordinary skill in the art that further compounds with the desired pharmacological properties can be prepared in an analogous manner, and that the disclosed compounds can also be obtained from different starting compounds via different chemical reactions. Similarly, different pharmaceutical compositions may be prepared and used with substantially the same result. Thus, however detailed the foregoing may appear in text, it should not be construed as limiting the overall scope hereof; rather, the ambit of the present invention is to be governed only by the lawful construction of the appended claims.

I claim:

1. A method of treating ocular hypertension which comprises administering topically to a mammal having ocular hypertension a therapeutically effective amount of a compound represented by formula II:
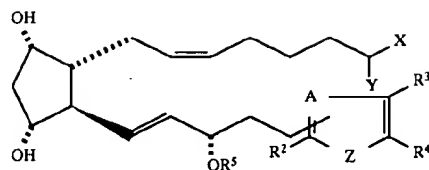

wherein the hatched segments represent α bonds, the solid triangle represents a β bond, wavy line attachments indicate either the alpha (α) or beta (β) configuration; R^1 is hydrogen or a lower alkyl radical having up to six carbon atoms, X is selected from the group consisting of —OR^1 and —$N(R^1)_2$, Y is =O or represents 2 hydrogen radicals;

Z is selected from the group consisting of O and S, A is selected from the group consisting of —CH, and C, R^2 is selected from the group consisting of hydrogen, lower alkyl or alkoxy having from 1 to 6 carbon atoms, trifluoro methyl, COR_1, $COCF_3$, SO_2NH_2, NO_2 and CN, R^3 and R^4 are selected from the group consisting of hydrogen, halogen, lower alkyl or alkoxy having from 1 to 6 carbon atoms trifluoromethyl, COR_1, $COCF_3$, SO_2NH_2, and CN, provided however at least one of R^2, R^3 or R^4 must be halogen or alkyl.

2. The method of claim 1 wherein said compound is represented by formula III:

wherein R⁵ is hydrogen or methyl.

3. The method of claim 2 wherein X is —OH or —NH₂.

4. The method of claim 2 wherein Y is =O and X is —OH.

5. The method of claim 2 wherein Y is =O and X is —NH₂.

6. The method of claim 2 wherein Z is S.

7. The method of claim 6 wherein at least one of R^2, R^3 and R^4 are selected from the group consisting of halogen, lower alkyl having from 1 to 4 carbon atoms and lower alkoxy having from 1 to 4 carbon atoms.

8. The method of claim 6 wherein at least one of R^2, R^3 and R^4 is selected from the group consisting of chloro and bromo.

9. The method of claim 6 wherein at least one of R^2, R^3 and R^4 are chloro.

10. The method of claim 9 wherein at least two of R^2, R^3 and R^4 are chloro.

11. The method of claim 2 wherein Y is =O, X is —OH or —NH₂ and Z is S.

12. The method of claim 11 wherein at least one of R^2, R^3 and R^4 is selected from the group consisting of chloro and bromo.

13. The method of claim 11 wherein at least one of R^2, R^3 or R^4 are bromo or at least two of R^2, R^3 or R^4 are chloro.

14. The method of claim 13 wherein said compound is 7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(2-(4-bromo) thienyl)-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

15. The method of claim 13 wherein said compound is 7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(3-(2,5-dichloro) thienyl-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

16. The method of claim 13 wherein said compound is 7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(2-(5-bromo) thienyl)-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

17. The method of claim 13 wherein said compound is 7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(2-(3-chloro) thienyl)-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

18. The method of claim 13 wherein said compound is 7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(3-(2-chloro) thienyl-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

19. The method of claim 13 wherein said compound is 7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(3-(2,5-dichloro) thienyl)-1E-pentenyl)cyclopentyl]-5Z-heptenamide.

20. The method of claim 11 wherein at least one of R^2, R^3 or R^4 is a lower alkyl radical having from 1 to 4 carbon atoms.

21. The method of claim 20 wherein at least one of R^2, R^3 or R^4 are ethyl, propyl or butyl.

22. The method of claim 21 wherein said compound is 7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(2-(5-ethyl)-thienyl) -1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

23. The method of claim 21 wherein said compound is 7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(2-(5-propyl) thienyl-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

24. The method of claim 22 wherein said compound is 7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(2-(5-butyl)thienyl- 1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

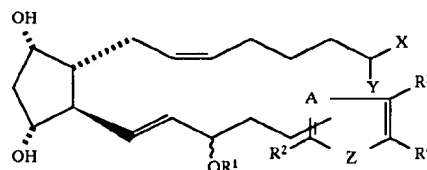25. An ophthalmic solution comprising a therapeutically effective amount of a compound of formula I, as defined in claim 1, or a pharmaceutically acceptable salt thereof, in admixture with a non-toxic, ophthalmically acceptable liquid vehicle, packaged in a container suitable for metered application.

26. The ophthalmic solution of claim 25 wherein said compound is a compound of Formula III.

27. A pharmaceutical product, comprising a container adapted to dispense the contents of said container in metered form; and an ophthalmic solution in said container comprising a compound of formula I as defined in claim 1, or a pharmaceutically acceptable salt thereof, in admixture with a non-toxic, ophthalmically acceptable liquid vehicle.

28. The product of claim 27 wherein said compound is a compound of Formula III.

29. The compound represented by Formula II:

wherein the hatched segments represent α bonds, the solid triangle represents β bond, wavy line attachments indicate either the alpha (α) or beta (β) configuration: A is selected from the group consisting of —CH and C, R^1 is hydrogen or a lower alkyl radical having up to six carbon atoms, R^2 is selected from the group consisting of hydrogen, halogen lower alkyl or alkoxy having from up to six carbon atoms, trifluoromethyl, COR_1, $COCF_3$, SO_2NH_2, NO_2 and CN, R^3 and R^4 are selected from the group consisting of hydrogen, halogen, lower alkyl or lower alkoxy having up to six carbon atoms, trifluoromethyl, COR_1, $COCF_3$, SO_2NH_2, NO_2 and CN, provided at least one of the R_2, R_3 or R_4 must be halogen or alkyl, Y is =O and X is —OH or —NH₂ and Z is S.

30. The compound of claim 29 wherein at least one of R^2, R^3 and R^4 are selected from the group consisting of halogen, lower alkyl having from 1 to 4 carbon atoms and lower alkoxy having from 1 to 4 carbon atoms.

31. The compound of claim 29 wherein at least one of R^2, R^3 and R^4 is selected from the group consisting of chloro and bromo.

32. The compound of claim 29 wherein at least one of R^2, R^3 and R^4 are chloro.

33. The compound of claim 32 wherein at least two of R^2, R^3 and R^4 are chloro.

34. The compound of claim 31 wherein at least one of R^2, R^3 and R^4 is selected from the group consisting of chloro and bromo.

35. The compound of claim 29 wherein at least one of R^2, R^3 or R^4 are bromo or at least two of R^2, R^3 or R^4 are chloro.

36. The compound of claim 35 wherein said compound is 7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(2-(4-bromo) thienyl)-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

37. The compound of claim 35 wherein said compound is 7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(3-(2,5-dichloro) thienyl-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

38. The compound of claim 35 wherein said compound is 7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(2-(5-bromo) thienyl)-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

39. The compound of claim 35 wherein said compound is 7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(2-(3-chloro) thienyl)-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

40. The compound of claim 35 wherein said compound is 7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(3-(2-chloro) thienyl-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

41. The compound of claim **35** wherein said compound is 7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(3-(2,5-dichloro)thienyl)-1E-pentenyl)cyclopentyl]-5Z-heptenamide.

42. The compound of claim **29** wherein at least one of R^2, R^3 or R^4 is a lower alkyl radical having from 1 to 4 carbon atoms.

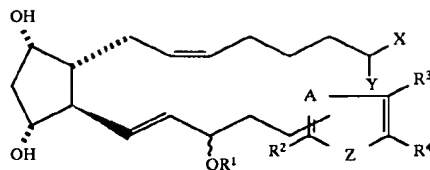**43.** The compound of claim **42** wherein at least one of R^2, R^3 or R^4 are ethyl, propyl or butyl.

44. The compound of claim **43** wherein said compound is 7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(2-(5-ethyl)-thienyl)-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

45. The compound of claim **43** wherein said compound is 7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(2-(5-propyl)thienyl-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

46. The compound of claim **43** wherein said compound is 7-[3α,5α-Dihydroxy-2-(3α-hydroxy-5-(2-(5-butyl)thienyl-1E-pentenyl)cyclopentyl]-5Z-heptenoic acid.

47. A method of treating glaucoma which comprises administering topically to a mammal having glaucoma a therapeutically effective amount of a compound represented by formula II:

wherein the hatched segments represent α bonds, the solid triangle represents β bond, wavy line attachments indicate either the alpha (α) or beta (β) configuration: R^1 is hydrogen or a lower alkyl radical having up to six carbon atoms, Z is selected from the group consisting of O and S, X is selected from the group consisting of —OR^1 and —$N(R^1)_2$, Y is =O or represents hydrogen radicals, A is selected from the group consisting of —CH, and C, R^2 is selected from the group consisting of hydrogen, lower alkyl or alkoxy having from 1 to 6 carbon atoms, trifluoromethyl, COR_1, $COCF_3$, SO_2NH_2, NO_2 and CN, R^3 and R^4 are selected from the group consisting of hydrogen, halogen, lower alkyl or lower alkoxy having from 1 to 6 carbon atoms, trifluoromethyl, COR_1, $COCF_3$, SO_2NH_2, NO_2 and CN;

provided however at least one of the R_2, R_3 or R_4 must be halogen or alkyl.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 5,834,498
DATED : November 10, 1998
INVENTOR(S) : Burk

It is certified that error appears in the above-indentified patent and that said Letters Patent is hereby corrected as shown below:

Column 9, line 4; delete "1.86-10H" and replace with —1.86-2.35 (M, 10H)—

Column 10, line 16; delete "3α" (second occurrence)" and replace with —3β—

Column 10, line 29; delete "^{4}" and insert in place thereof —4—

Column 10, line 35, delete "^{2}" and insert in place thereof —2—

Column 10, line 50, delete "3α" (second occurrence)" and insert in place thereof —3β—

Column 13, line 3, delete "5.4" and insert in place thereof —5.04—

Signed and Sealed this

Tenth Day of August, 1999

Attest:

Q. TODD DICKINSON

Attesting Officer   Acting Commissioner of Patents and Trademarks